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Part II

Office of Science and Technology Policy

Proposal for a Coordinated Framework for Regulation of Biotechnology; Notice

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

Proposal for a Coordinated Framework for Regulation of Biotechnology

AGENCY: Executive Office of the President, Office of Science and Technology Policy.

ACTION: Notice for public comment.

SUMMARY: The purpose of this Federal Register notice is to provide a concise index of U.S. laws related to biotechnology, to clarify the policies of the major regulatory agencies that will be involved in reviewing research and products of biotechnology, to describe a scientific advisory mechanism for assessment of biotechnology issues, and to explain how the activities of the Federal agencies in biotechnology will be coordinated.

DATE: Comments must be received on or before April 1, 1985.

Public Participation: The Cabinet Council Working Group on Biotechnology through the Office of Science and Technology Policy, is seeking the advice of individuals, public interest groups, industry and academia on all aspects of this publication. The Working Group welcomes candid assessments of the process and the policy as well as questions raised regarding the scope of the proposal.

The intention of the Working Group is to republish this material in final form as soon as possible following the close of the comment period. This will assure that well understood regulatory policy and process are established in timely manner to enable a beneficial industry to proceed safely and efficiently.

Information submitted as comments to EPA on this notice may be claimed confidential by marking any part or all of that information as "Confidential Business Information." Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR Part 2. A sanitized copy of any material containing Confidential Business Information must be provided to EPA by the submitter for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice.

ADDRESS: Comments specific to the EPA, USDA, or FDA policy statements should be addressed to:

EPA: Docket #OPTS 00049, Document Control Officer (TS–793), Office of Toxic Substances, Environmental Protection Agency, Room E–409, 401 M Street, SW., Washington, D.C. 20460

USDA: Docket #APHIS 00049, Ms. Karen Darling, Deputy Assistant Secretary, Marketing and Inspection Services, U.S. Department of Agriculture, Room 242–E, Administration Building, 12th and Independence Avenue, SW., Washington, D.C. 20250

FDA: Docket #84N–0431, Dockets Management Branch, Food and Drug Administration (HFA–305), Room 4–62, 5600 Fishers Lane, Rockville, MD 20857

Any other comments should be provided to the following address: Dr. Bernadine Healy Bulkley, Deputy Director, Office of Science and Technology Policy, Executive Office of the President, NEOB—Room 5005, Washington, D.C. 20506.

Jerry D. Jennings,

Executive Director, Office of Science and Technology Policy.

December 21, 1984.

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Introduction

Only forty years ago, DNA was discovered to be the repository of genetic information. This discovery has been followed by an explosion in our understanding and ability to manipulate the gene as manifest by the new commercial biotechnology which has introduced a new and profound dimension into the field of classical genetics. Today, new techniques for manipulating genetic information offer exciting advances, as remarkable as the discovery of antibiotics or the computer chip.

While some techniques of biotechnology are not new—the use of yeast in baking and brewing began around 6000 B.C.—the most recently developed techniques are far more sophisticated. Modern biotechnology promises to benefit many fields of human endeavor by offering new services and a wide variety of products superior to those currently available because they will be more effective, convenient, safer, or more economical. Biotechnology already has successfully produced new drugs and improved existing drugs such as human insulin, interferons and vaccines. Exciting research is underway in agricultural applications to enhance plant and animal productivity to help feed the world's people. Within reach of commercial applicability are products to diagnose, prevent and treat animal diseases, to improve animal breeds and to improve specific plant characteristics. Microorganisms have also been developed in research laboratories to degrade pollutants, enhance oil recovery, convert biomass to energy, leach minerals, and concentrate metals. With this diversity of applications, biotechnology will alleviate many problems of disease and pollution and increase the supply of food, energy, and raw materials.

The United States is now the world leader in biotechnology. This leadership is derived from a strong science base, a vigorous entrepreneurial spirit and availability of venture capital. New uses of biotechnology have created intense domestic and international competition. Several other nations have elevated the development of biotechnology to a national priority. The tremendous potential of biotechnology to contribute to the nation's economy in the near term, and to fulfill society's needs and alleviate its problems in the longer term, makes it imperative that progress in biotechnology be encouraged.

While the potential benefits of biotechnology are widely acknowledged, legitimate concerns about safety have also been raised as additional products of biotechnology move from contained research laboratories into full contact with the public and the environment through commercial testing and applications in the environment. For example, concerns have been raised about the effect of genetic manipulations on the potential virulence of altered microorganisms, or the ability of new organisms to obtain a selective advantage. Certainly both the safety and effectiveness of new processes and products must be central issues in the design of new scientific developments or technological innovations. Accordingly, it is incumbent upon the government, the business community, and the public to take responsible and timely measures to insure that the public health and the environment are protected and that societal concerns are promptly addressed.

The Administration, recognizing its responsibility to confront the special concerns that surround modern biotechnology, formed an interagency working group under the White House Cabinet Council on Natural Resources

and the Environment. The fundamental purpose of the Working Group is to insure that the regulatory process adequately considers health and environmental safety consequences of the products and processes of the new biotechnology as they move from the research laboratory to the marketplace. The Working Group recognizes the need for a coordinated and sensible regulatory review process that will minimize the uncertainties and inefficiencies that can stifle innovation and impair the competitiveness of U.S. industry. It recognizes that not only should approaches be consistent from agency to agency and within each agency from application to application, but also that regulatory decisions should be based upon the best available science.

The importance of addressing the emerging commercial aspects of biotechnology in a coordinated and timely fashion is captured in the recent report by the Congressional Office of Technology Assessment which warned: "Although the United States is currently the world leader in both basic science and commercial development of new biotechnology, continuation of the initial preeminence of American companies in the commercialization of new biotechnology is not assured." [1]

The Working Group recognizes that the manner in which regulations for biotechnology are implemented in the United States will have a direct impact on the competitiveness of U.S. producers in both domestic and world markets and the future development of basic science. Thus, the Working Group has endeavored to develop a coherent and sensible regulatory process, one based on the best available scientific facts and intended to minimize uncertainties, delays, overlaps, and inconsistencies. Attention will be paid also to international harmonization. The United States is seeking to promote scientific cooperation, mutual understanding of regulatory approaches and international agreement on a range of common technical problems such as the development of consistent test guidelines, laboratory practices and principles for assessing potential risks. The U.S. also is committed to reducing barriers to trade in biotechnology. U.S. regulatory agencies will provide similar treatment to domestic and foreign products with regard to their regulations and approval procedures. Barriers to trade of biotechnology products can only be avoided if the U.S. and other nations join together in working toward this goal. In achieving national consistency and international harmonization, regulatory decisions can be made in a socially responsible manner, protecting human health and the environment, allowing U.S. producers to remain competitive and, most importantly, assuring that everyone will reap the benefits of this exciting biological revolution.

[1] *Commercial Biotechnology*, "An International Analysis," Office of Technology Assessment, Pg. iii., 1984.

Regulation of Biotechnology Processes and Products

In response to concerns of the scientific community in the early 1970s, the Federal Government sponsored a conference to explore the risks and benefits of recombinant DNA (rDNA) research. In 1974 the National Institutes of Health (NIH) chartered the Recombinant DNA Advisory Committee (RAC) to provide scientific advice and in 1976 developed the NIH Guidelines for Research Involving Recombinant DNA Molecules. It was reasoned that a cautious approach to this research was essential to assure safety while still fostering the advancement of this new technology. These guidelines have allowed research to flourish within appropriate constraints. Experience gained in rDNA laboratory research has mitigated many of the concerns about risk, thus allowing modification of the original guidelines and oversight mechanisms.

Almost a decade later as the pace of commercial application has accelerated, this new initiative was undertaken to review regulatory requirements and to articulate policy for biotechnology products. In April 1984, the Cabinet Council on Natural Resources and the Environment established an interagency working group to study and coordinate the government's regulatory policy for these products.[2] The group was asked to:

1. Review the regulatory requirements which have been applied to commercialized biotechnologies.

2. Identify existing laws and regulations that may be applicable to biotechnology.

3. Review the function of the NIH Recombinant DNA Advisory Committee and its role in biotechnology commercialization and safety regulation.

4. Clarify the regulatory path that a company with a new product would follow to meet Federal health and safety requirements.

5. Determine whether current regulatory requirements and Federal review are adequate for new products.

6. Develop specific recommendations for administrative or legislative actions to provide additional regulatory review if warranted, while maintaining flexibility to accommodate new developments.

7. Review court rulings regarding the granting of patents for biotechnology.

8. Review other Federal actions such as support of basic research and training, U.S. patents and trade laws, and other policy issues which affects commercialization and U.S. competitive position vis-a-vis international firms.

The results of the interagency effort to date are reflected in the publication of this notice for public review and comment. These include: (1) Regulatory matrix: a concise index of the current regulatory requirements that might be applicable to biotechnology; (2) Policy statements: a compilation of proposed statements of policy that describe how the U.S. Department of Agriculture, the Environmental Protection Agency and the Food and Drug Administration intend to apply their existing regulatory authorities to biotechnology products; (3) A Scientific Advisory Mechanism: a coordinated structure of scientific review to promote consistent risk assessment within statutory confines; and (4) Glossary: a glossary of terms used in the policy statements.

Given the evolving nature of biotechnology, the Working Group will continue to meet to review the ongoing process. If regulatory gaps emerge and the process is not responding to public concerns, the Working Group will make recommendations for either administrative reform or additional legislative authority.

1. Regulatory Matrix

The matrix outlines laws, regulations and guidelines that may be applicable to biotechnology products at some point in research, development, marketing, shipment, use, or disposal. To aid in understanding current requirements, the matrix has been divided into seven parts which have been cross-referenced when necessary:

I. Licensing and other premarketing requirements;

II. Post-marketing requirements;

III. Export controls;

IV. Research and information gathering;

V. Patents;

[2] The member agencies include: Departments of Interior, Justice, State, Agriculture, Commerce, Defense, Energy, Health and Human Services, and Labor; Environmental Protection Agency; Council on Environmental Quality; Council of Economic Advisors; Office of Management and Budget; Office of Policy Development; the National Science Foundation; Office of the U.S. Trade Representative; and the Office of Science and Technology Policy.

VI. Air and water emissions standards; and

VII. Requirements for Federal agencies.

The matrix will be reviewed annually and updated as necessary.

2. Policy Statements

Individual "Statements of Proposed Policy" have been developed by the three regulatory agencies—FDA, USDA and EPA—that will be involved most extensively in oversight of research and industrial engaged in product development. These statements do not describe detailed regulatory requirements, but rather the general policy framework within which regulatory decisions will be made. They attempt to provide a clear understanding of how regulatory agencies will approach this evolving technology. At present the regulatory authorities that are in place appear to accommodate these new products.

The responsibilities of EPA, FDA and USDA are determined by statute (see the Matrix of Federal Authorities elsewhere in this notice), and are generally based upon key characteristics or uses of the end products. When new types of products are developed, such as will be the case with biotechnology, each agency must develop and apply certain rules for determining whether its statutes apply with possible modification of existing rules. For example, FDA must determine whether products containing genetically engineering microorganisms constitute food additives, drugs, or other products subject to FDA approval, EPA whether they are pesticides or industrial products, and USDA whether they are plant pests, animals biologicals, or other agricultural products subject to its authority. These decisions must be consistent with the statutory requirements of the laws each agency administers.

Regardless of the criteria used to determine whether a product is within the responsibility of a given agency, all three agencies will approach the review of biotechnology products and processes in similar ways. All conduct their assessments on a case-by-case basis, employing internal staff, consultants, and expert advisory committees (described below). Each considers the ultimate safety of the product as a primary concern; other issues, such as efficacy, may also be considered. Also, each agency develops product review criteria and procedures which are consistent with its historical experience and scientific data bases developed from reviewing other products with similar uses.

EPA, FDA and USDA are committed to working together and with other members of the Cabinet Council Working Group to coordinate and improve the development of appropriate and useful scientific evaluation methods and administrative procedures for genetically engineered organisms and their products. All are striving for a balanced approach supported by sound science and incorporating the latest scientific and technological information. The statements of proposed policy which each has prepared and which are issued in this notice are viewed as among the first steps toward that goal.

3. Scientific Advisory Mechanism

The importance of the highest caliber scientific advice to the decision-making process for oversight of biotechnology is undisputed. NIH's experience with its RAC is an example of the value of using distinguished scientists to participate in the assessment of risk of new projects or proposals involving genetic manipulation. The experience of the RAC over the past ten years serves as a valuable model to the Working Group in structuring the proposed scientific review coordinating mechanism.

With the evolution of biotechnology and its increasing commercialization, the complexity and scope of scientific review broadens and the existing mechanisms for scientific review must be expanded. The Working Group proposes an adjunctive scientific advisory mechanism that will accommodate the needs of individual agencies and provide a central focus for scientific advice on biotechnology issues. It affords maximal opportunity to achieve scientific consensus and retains the flexibility in scientific policy guidance that has characterized the existing NIH RAC. In addition, it can be implemented in a short time.

4. Glossary

The glossary included at the end of this notice is intended to provide definitions for terms appearing in the policy statements to assist the reader in reviewing the notice. The definitions are not to be considered legally binding on any Federal agency and may be revised as needed.

Interagency Coordination of Risk Management and Regulation in Biotechnology

In addition to coordination of scientific review, the Working Group recognizes the need for coordination of the regulatory activities of the federal government. An interagency committee is needed to foster timely and coordinated decision making via interagency communication on matters of regulation; discuss matters of jurisdiction among agencies; serve as a mechanism by which agencies can raise public and concerns; and consider generic approaches for translating risk industry assessment information into policy decisions.

The Cabinet Council Working Group also recognizes the need for this continuing coordinated mechanism also to address the broader issues within the regulatory process itself. Although at the present time existing statutes seem adequate to deal with the emerging processes and products of modern biotechnology, there are always potential problems and deficiencies in the regulatory apparatus in a fast moving field. We believe this interagency coordinating committee should monitor the changing scene of biotechnology and serve as a means of identifying potential gaps in regulation in a timely fashion, making appropriate recommendations for either administrative or legislative action.

For the time being the Cabinet Council Working Group can serve these needs. When its activities are concluded, an interagency coordinating committee for Biotechnology would, if still needed, be established to continue this effort.

BILLING CODE 6560-50-M

BIOTECHNOLOGY AUTHORITIES

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
I. LICENSING AND OTHER PREMARKETING REQUIREMENTS					
Food, Drug and Cosmetic (FD&C) Act (21 USC 301-392) Regulations: 21 CFR Parts 1, 71, 171, 314, 514, 571, 807	Premarketing approval required for: drugs -- Sec. 505 medical devices -- Sec. 515 food additives -- Sec. 409 color additives -- Sec. 706 animal drugs -- Sec. 512	All human and animal drugs and human devices, food additives, animal feed additives, and color additives	HHS-FDA	Certain EPA statutes specifically exclude FD&C Act products. EPA sets tolerance levels for pesticide residues in the food chain. FDA provides human tolerance levels for animal drugs in food chain meat and poultry to the USDA-FSIS. Animal and human biologics are regulated under the Virus-Serum-Toxin Act (VST Act), a USDA statute, and the Public Health Service Act, respectively. FDA decisions are subject to National Environmental Policy Act (NEPA).	From the beginning of clinical research to premarketing approval takes for: human drugs: 7-10 years animal drugs: 3-5 years devices: 2-5 years direct food additives: 5-7 years indirect food additives: 3-5 years color additives: 5-9 years Important: FDA regulates biotechnology on a product-by-product basis. FDA will not be restructuring the process to regulate the products of biotechnology or the manufacturers of those products.
Public Health Service (PHS) Act Section 351(a) (42 USC 262) Regulations: 21 CFR 600-680	Licensing for marketing required for human biologics	Human biologics	HHS-FDA	USDA-APHIS licenses animal biologics produced by interstate manufacturers. FDA decisions are subject to NEPA.	The research use of investigational new drugs is regulated under the FD&C Act. From the beginning of clinical research to license takes approximately 2-8 years depending on the type of biologic, but 6-8 is more common.
"Points to consider in the characterization of cell lines used to produce biologicals"	FDA technical guidance for new product appproval	Human drugs and biologics	HHS-FDA		
"Points to consider in the manufacture of Monoclonal Antibody Products for Human Use"	FDA technical guidance for new product approval	Human drugs and biologics	HHS-FDA		FDA reviews the adequacy of testing of all products on a case-by-case basis.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
"Points to consider in the production and testing of new drugs and biologicals produced by rDNA technology"	FDA technical guidance for new product approval	Human drugs and biologics	HHS-FDA		New Investigational New Drug (IND) and biological licenses and/or new drug approvals are required currently with rDNA technology even if the active substance is identical in molecular structure to a previously approved product.
PHS Act Section 353 (42 USC 263a) Regulations: 42 CFR 74	License required for clinical laboratories engaged in interstate commerce	Laboratory services	HHS-CDC HHS-Health Care Financing Admin.		To meet licensure requirements, laboratories must meet proficiency testing, quality control, and personnel standards.
Virus-Serum-Toxin Act (21 USC 151-158) Regulations: 9 CFR 101-117 and 122-123	License required for any virus, serum, toxin, or analogous product intended for use in treatment of domestic animals which are shipped interstate or imported. Regulations contain standards of efficacy, purity, safety and potency. They also contain labeling provisions.	9 CFR 101.2(w) defines "biological products" to mean "all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live microorganisms, killed microorganisms and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases of animals."	USDA-APHIS	USDA decisions are subject to NEPA. The definition of drugs in the FD&C Act includes biological products. The FD&C Act (21 USC 391) and its regulations exempt biological products regulated under the VST Act.	USDA's licensing policy for conventional or rDNA derived veterinary biologics is on a product-by-product basis, and requires that all license applicants for rDNA products comply with the NIH "Guidelines for Research Involving Recombinant DNA Molecules."
USDA's Licencing Policy for Biologicals Produced by rDNA	USDA technical guideline reviewing production and test considerations for evaluating rDNA product license applications.	Veterinary biologics and diagnostics	USDA-APHIS		Each veterinary biologic product is reviewed as a single entity. USDA evaluates each license application for conventional or rDNA biologics to ensure purity, potency, safety, and efficacy.
Veterinary Services Memorandum Number 800.68	USDA policy and procedures for new product license applicants	Veterinary biologics and diagnostics	USDA-APHIS		Technical guidelines used for licensing products developed through rDNA or hybridoma technology.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Memorandum of Understanding between USDA and FDA for Defining Jurisdiction of Animal Drugs. (See 47 FR 26458, June 18, 1982)	Agreement between APHIS and FDA regarding responsibility for regulating animal biologic products as biologics under the VST Act or as drugs under the FD&C Act.	Veterinary biologics or drugs	HHS-FDA USDA-APHIS		
Toxic Substances Control Act (TSCA) (5 USC 2601-2929)	TSCA applies to "chemical substances" defined as "any organic or inorganic substance of a particular molecular identity including...any combination of such substances ...occurring in nature..." TSCA requires premanufacture review of new chemical substances and authorizes regulation of new and existing substances.	Industrial chemicals produced by genetically engineered organisms or by-products (e.g., enzymes); organisms used in general industrial, commercial, and consumer applications, such as water pollution control, mineral leaching, drain cleaning, etc.; organisms used to make TSCA or Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) chemicals	EPA, agencies that manufacture "chemical substances" for commercial purposes.	Drugs, biologics, foods, food additives, cosmetics, pesticides and tobacco and tobacco products are excluded from TSCA review.	Provides broad range of authority over "chemical substances."
Section 5(a)(1)(A)	Requires submission of premanufacture notice (PMN) for "new chemical substances"	New products (including organisms) used for purposes listed above	EPA		Mandatory requirement; 90-day review, extendable for "good cause" to 180 days. EPA must make a finding of potential risk or exposure to regulate. R&D in small quantities (including small quantities of biotechnology R&D) are exempt from PMN. "Small quantities" as defined by rule would exempt most field testing.
Section 5(h)(3)	Exempts research and development activities from PMN requirements	Organisms and other substances used in the lab; products sold solely for R&D use (e.g., restriction enzymes)	EPA		
Section 5(a)(1)(B)	Authorizes EPA to require by rule reporting before "chemical substances" are used for "significant new uses"	TSCA chemicals proposed for new use	EPA		Discretionary. "Significant new uses" must be defined by rule. No regulations currently in place that affect biotechnology.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Regulations: 40 CFR 720	PMN requirements	TSCA Chemicals	EPA, agencies that manufacture "new chemical substances" for commercial purposes.		Interprets mandatory statutory requirements.
Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (7 USC 136-136y)	Requires registration of pesticides before distribution or use (pesticide broadly defined as "any substance or mixture...intended for preventing, destroying, repelling or mitigating any pest, and ...intended for use as a plant regulant, defoliant, or dessicant.")	Biological pesticides (e.g., microorganisms or their chemical products). Includes INA bacteria.	EPA, USDA-FSIS, HHS-FDA	EPA sets tolerance levels for pesticide residue in the food chain which FDA and USDA-FSIS enforce.	Pesticides defined to include living organisms. EPA review period could vary from one to several years. Fourteen microbial pesticides (non-engineered) have been approved.
Section 3(c)(2)(A)	Authorizes EPA to publish "guidelines" specifying kinds of information needed for registration.		EPA		
Section 5	Authorizes EPA to issue experimental use permits for limited uses before registration.		EPA		120 day review period; can be extended.
Section 25(b)	Authorizes EPA to exempt a pesticide from registration.		EPA, USDA-APHIS	USDA has responsibility for higher plants and animals that are considered pesticides (40 CFR 162.5(c)(4)).	Higher plants and animals and certain pheromone attractants have been exempted.
Regulations: 40 CFR 158	Data requirements for pesticide registration including genetically modified microbial pesticides	Microbial pesticides	EPA	Section 3 of FIFRA	Includes data requirements for microbial pesticides. Testing requirements are tiered, with more complicated tests required where certain criteria are met. Additional requirements for genetically modified and other microbial pesticides determined on a case-by-case basis.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
40 CFR 162	Pesticide registration regulations	Microbial pesticides	EPA, USDA-APHIS DOI	Section 3 of FIFRA; Biological control agents regulated by USDA, DOI, or other Federal agencies under express statutory authority not included.	Applies to viruses, bacteria, protozoa, fungi, etc., used as pesticides. Does not apply to higher plants and animals.
40 CFR 172	Experimental use permit regulations	Field-tested microbial pesticides	EPA	Section 5 of FIFRA	120 day review period which can be extended; for land uses, generally only need permit if test covers more than 10 acres, but EPA has authority to require permits for less than 10 acres under certain circumstances.
"Microbial Pesticides; Interim Policy on Small Scale Field Testing" (49 FR 40659 (1984))	EPA policy requiring notification prior to small scale field tests with certain microbial pesticides	Microbial pesticides containing nonindigenous or genetically altered microorganisms	EPA	Section 5 of FIFRA and 40 CFR 172	Applies to tests conducted on 10 or less acres of land or 1 or less acre of water (i.e., small scale field testing)
Guidelines: Pesticide (Subdivision M) Assessment Guidelines (October (1982))	Provides guidelines for developing data required under 40 CFR 158.	Microbial pesticides	EPA		
Reorganization Plan No. 3 of 1970, Section 2(4)(5 USCA App.)	Authorizes EPA to establish tolerances for pesticide residues in food chain	Pesticide products used so as to result in residues in food chain	EPA, HHS-FDA, USDA-FSIS	FD&C Act Sections 406, 408, 409 EPA sets pesticide standards which are enforced by FDA and USDA.	
Regulations: 40 CFR 162.7(d)(3)(v) and 162.18-4(a)(4)	Requires tolerances before registration	Pesticides to be registered for food or animal feed use	EPA, HHS-FDA, USDA-FSIS		
Guidelines:					
"Guidelines for Research Involving Recombinant DNA Molecules" (49 FR 46266 (1984))	Specifies practices for constructing and handling rDNA molecules and organisms and viruses containing rDNA molecules. Compliance is required for institutions that receive support for rDNA research from NIH.	All rDNA research conducted by institutions receiving NIH support as well as NIH itself.	All involved in rDNA research, primarily HHS and USDA. Administered by HHS-NIH with the advice of the rDNA Advisory Committee (RAC)	Biotechnology R&D exempt from PMN requirement of TSCA.	Voluntary compliance for institutions that receive no NIH rDNA research funding.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
II. POST MARKETING REQUIREMENTS A. Occupational Safety					
"Biosafety in Microbiological and Biomedical Laboratories"	CDC/NIH manual which describes combinations of standard and special microbiological practices, safety equipment, and facilities that constitute biosafety levels 1-4 and serve as recommendations for working with a variety of infectious agents in the lab.	All clinical, public health, and private diagnostic labs and research labs using pathogenic microorganisms.	All involved in diagnostic public health and research HHS, USDA, EPA		Voluntary compliance for all Federal, State, and private labs.
Occupational Safety and Health Act (29 USC 651 et seq.)	Regulation of the workplace to assure that no employee will suffer diminished health as a result of conditions in the workplace; authority to publish standards with which employers must comply; authority to fund research and development; authority to "describe exposure levels" (risk assessment). No license or premarket approval required.	Exposure to inorganic and organic chemicals and microbials.	DOL-OSHA, HHS-CDC-NIOSH	In setting standards, the Secretary of Labor may use information provided by "an interested person" including the NIEHS and NCI of NIH, the NBS of Commerce, NIOSH of CDC, the NTP of HHS. NIOSH does exposure levels. NIOSH recommends standards to OSHA. OSHA has the ability to regulate any workplace so that, no matter who approves a given technology or enviromental release, OSHA can intervene to protect employees. Note: The Mine Safety and Health Act will apply in similar fashion in those cases where biotech is used to extract minerals.	The statute uses several adjectives that are subject to interpretation such as serious physical harm and material impairment of health. The Secretary of Labor may grant a waiver to standards under certain specific and narrowly defined conditions. Standards may be effective immediately in cases of imminent hazard. Important: States have the right to enforce their own standards where no Federal standards exist and they have the right to administer Federal standards under plans approved by the Secretary of Labor.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Regulations:					
29 CFR 1900-1910 Workplace Standards	Sets regulatory standards for specific workplace hazards	Primarily toxic chemicals	DOL-OSHA HHS-CDC-NIOSH	NIOSH recommends standards to OSHA	There is no general industry standard requiring compliance in the biotech area. A standard may be developed for each engineered area.
30 CFR 11 Workplace Respirator Standards	Sets a regulatory standard for respirators	Respirable toxins	HHS-CDC-NIOSH DOL-Mine Safety and Health Admin. (MSHA)	OSHA and MSHA require adherence to respirator standards	NIOSH has a regulatory role here.
29 CFR 1910.20 Access to Employee Exposure and Medical Records	Provides access to plant information on toxic substances and harmful physical agents and to medical monitoring data related to exposures	Toxic substances and physical and biological agents	DOL-OSHA HHS-CDC-NIOSH		
29 CFR 1910.1200 Hazard Communication	Requires manufacturers and importers to evaluate hazards of their products and communicate this information to employees through labels, material safety data sheets and training	Toxic substances	DOL-OSHA		Could include biological agents
TSCA Section 6	Authorizes EPA to regulate the manufacture, processing, distribution in commerce, use, and disposal of "chemical substances"	TSCA "chemical substances"	EPA, CPSC, OSHA, DOT		Discretionary authority can be exercised if EPA finds a substance "will present" an unreasonable risk. Can be used to impose controls through all phases of manufacture, processing, use and disposal. Unlike PMN authority (Sec. 5(a)(1)(A)), Section 6 can be applied to R&D substances. No regulation affecting biotechnology in effect.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
B. Drug Manufacturing Practices					
FD&C Act Section 501(a)-(e) (21 USC 351) Regulations: 21 CFR 210, 211, 225, 226	FDA establishes "current good manufacturing practices" (CGMPs) for drug products through regulation that are mandatory for manufacturers	Drugs, human biologics, and medicated feeds	HHS-FDA		Certain aspects are also applicable to premarketing manufacture.
C. Hazardous Waste					
Comprehensive Environmental Response, Compensation, and Liability Act (Superfund Act) (42 USC 9601-9657)					
Sections 102, 103	Requires reporting of releases of "reportable quantities" of hazardous substances	Substances identified as hazardous under Sections 101 or 102	EPA-Nat'l Response Center		"Hazardous substance" refers to (1) certain substances regulated under the Clean Water Act, Clean Air Act, TSCA, and Resource Conservation and Recovery Act, and (2) any other substances that may present substantial danger to public health, welfare, or the environment and are listed by EPA under Section 102 of Superfund Act. Some genetically engineered organisms or byproducts could meet the latter test; none now listed.
Section 104	Provides health assessment and specific public health activities at superfund sites	Substances identified as hazardous under Sections 101 or 102	HHS-Agency for Toxic Substances & Disease Registry (ATSDR)		
Section 105	Requires EPA to develop National Contingency Plan (NCP) for cleanup of hazardous substances; must specify methods for cleanup (e.g., use of biological materials).	Products used to degrade hazardous substances.	EPA, other emergency response agencies (e.g., HHS-CDC, FEMA, DOT)		
Regulation: 40 CFR 300	National Contingency Plan	Products used to degrade hazardous substances	EPA, other emergency agencies		Regulation identifies criteria for responding to releases and lists use of microorganisms for waste treatment.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Resource Conservation and Recovery Act (RCRA) (42 USC 6901-6987)					
Section 3001	Authorizes EPA to list and identify hazardous waste with assistance from ATSDR and the National Toxicology Program (NTP)	Waste identified as hazardous.	EPA, HHS-ATSDR, NTP		Discretionary authority to list waste as hazardous; no living organisms now listed. However, a biotechnology waste could be listed if concern warrants. If mixed with listed hazardous waste or if they exhibit hazardous waste characteristics, biological wastes could be regulated as hazardous waste.
Sections 3002-3004	Standards applicable to generators, transporters, and owners and operators of facilities that treat, store, and dispose of hazardous waste.	Solid waste identified as hazardous waste under RCRA.	EPA, DOT	DOT's authority under Hazardous Materials Transportation Act overlaps EPA's RCRA authority, but DOT and EPA have memorandum of agreement to divide responsibilities. (45 FR 51645 (1980))	
Section 3005	Requires permits for treatment, storage, disposal of hazardous waste.	Waste identified as hazardous.	EPA, DOT		
Sections 4005(a) and 1008	Prohibits "open dumping" of solid wastes	Solid waste	EPA		Biological products or byproducts would be subject to the prohibition when disposed.
Regulations:					
40 CFR 260	Hazardous waste management system -- general requirements		EPA		
40 CFR 261	Identification and listing of hazardous waste		EPA		
40 CFR 260-267	Standards for generators, transporters, and owners or operators of facilities that treat, store, and dispose of hazardous waste.		EPA, DOT	DOT regulates transportation of hazardous "materials."	Would affect industries using biotechnology only to the extent they generated wastes identified as hazardous. No living organisms listed.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
40 CFR 270 Marine Protection, Research, and Sanctuaries Act (Ocean Dumping) (33 USC 1401-1445)	Hazardous waste permit program		EPA		
Section 102, 103	Prohibits ocean dumping without a permit, authorizes EPA to issue permits for dumping all materials except dredged materials and materials specifically prohibited by statute.	Microbial products used in pollution control; waste and byproducts from manufacture, use, etc.	EPA, Corps of Engineers	Corps of Engineers authorized to issue permits for dredged material.	
Regulations: 40 CFR 227-228	Criteria for approving permits; prohibits dumping of wastes containing living organisms that would endanger health or the environment; exempts dredged material from this prohibition.		EPA, Corps of Engineers		
D. Other Containment and Transportation Requirements					
Federal Meat Inspection Act (21 USC 601 et seq.) Regulations: 9 CFR 301 et seq.	Regulates, through mandatory inspection, the slaughtering, preparation, labeling, marking, distribution of meat and meat food products to prevent "adulterated" or "misbranded" meat and meat food products from entering commerce.	Meat and meat food products (specifically cattle, sheep, swine, goat, horse, mule, or other equine). See definition in 9 CFR 301.2 (tt) and (vv)	USDA-FSIS	FDA sets residue tolerance levels for animal drugs in food-chain animals. FDA's regulatory authority is found in 21 CFR 556.	Both the Federal Meat Inspection Act and the Poultry and Poultry Products Inspection Act determine whether regulated articles contain any "biological residues" (see definitions in 9 CFR 301.2 (22) and 381.1 (7), and contain specific recordkeeping, buying, selling, and transportation requirements affecting foreign, interstate, and intrastate commerce.
Poultry and Poultry Products Inspection Act (21 USC 451 et seq.) Regulations: 9 CFR 381	Regulates, through mandatory inspection, the slaughtering, preparation, distribution, disposition, marking, and labeling of poultry and poultry products to prevent "adulterated" or "misbranded" poultry and poultry products from entering commerce.	Poultry (specifically, any domesticated bird--chicken, turkey, ducks, geese, or guineas, whether live or dead) and poultry products. See definition in 9 CFR 381.1 (40) and (41).	USDA-FSIS		

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Hazardous Materials Transportation Act (49 USC 1801 et seq.) Regulations: 49 CFR 107, 171-177	Regulation of transportation of hazardous materials. Shippers must register with DOT. Authorizes halt of shipping immediately for "imminent hazard."	Etiologic agents	DOT-Ofc of Hazardous Materials Regulation	DOT consults with the ICC which is responsible for enforcement where it has authority. DOT has an agreement with EPA (RCRA) on duplicative authorities.	May regulate packing, labeling, and routing as well as the manufacture of packaging. Secretary may exempt shippers if they achieve a level of safety higher than the level of safety required or if no standard exists and public safety is maintained.
PHS Act Section 361 (42 USC 264) Regulations: 42 CFR 71-72	Authorizes regulation of introduction and control of communicable diseases, interstate transportation of etiologic agents and importation of etiologic agents and vectors.	Etiologic agents	HHS-CDC, FDA, NIH		The requirements of this regulation are in addition to and not in lieu of any other requirements of DOT, USDA, or EPA for importation or interstate transport.
Section 102, Organic Act of 1944, as amended, and the Act of April 6, 1937, as amended (7 USC 147a, 148, 148a-e) Regulations: 7 CFR 300-399	General authority to "carry out operations or measures to detect, erradicate, suppress, control, or to prevent or retard the spread of plant pests." Provides for inspection of plants and plant products offered for export.	"Plant pests" are defined as: "any living stage of any insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof, viruses, or any organisms similar to or allied with any of the foregoing, or any infectious substances which can directly or indirectly injure or cause disease or damage in any plants or parts thereof, or any processed, manufactured or other products of plants."	USDA-APHIS	EPA also has authority over organisms that could act as plant pests.	Authority extends to cooperative action with States or political subdivisions, farmers associations and similar associations, individuals and governments of Western Hemisphere Countries.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Federal Plant Pest Act, as amended (7 USC 150aa-jj) and Plant Quarantine Act, as amended (7 USC 151-164a, 166-167) Regulations: 7 CFR 300-399	General authority to regulate the importation into and the dissemination within the U.S. of plant pests, nursery stock, and other plants and plant products, and any product or article which may contain a plant pest at time of movement. Authority for USDA to import for scientific or experimental purposes any class of nursery stock, plants, fruits, vegetables, roots, bulbs, seeds, or other plant products for which importation may otherwise be forbidden.	"Plant pests" are defined to be consistent with the definition of "plant pests" in Sec. 102 of the Organic Act.	USDA-APHIS		Authority to bring civil and criminal actions for violations of the Act or regulations promulgated thereunder. USDA may stop, and without a warrant, inspect, search, seize, examine, destroy or otherwise dispose of specified articles found to be moving or to have been moved in interstate commerce or to have been brought into the U.S. in violation of the Act or of a quarantine or order. In extraordinary emergency situations, USDA may stop intrastate activity as well.
"Animal Quarantine Laws" (21 USC 102-105; 21 USC 111; 21 USC 114a-114h; 21 USC 115-130; 21 USC 134-134h 21 USC 135-135b) Regulations: 9 CFR 1-199	In general, the animal quarantine laws regulate the importation, exportation, and interstate movement of certain animals to prevent the introduction or spread of communicable diseases of animals or of the contagion of any contagious, infectious, or communicable disease of animals or/and live poultry.	21 USC 101-105 regulates cattle, sheep and other ruminants and all swine imported into or intended for export from the U.S. 21 USC 111 regulates that which could introduce or cause the dissemination in the U.S. of the contagion of any contagious, infectious, or communicable disease of animals and/or live poultry.	USDA-APHIS		

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Federal Noxious Weed Act of 1974 (7 USC 2801-2813) Regulations: 7 CFR 360	Authority to issue permits to regulate the movement of noxious weeds into or through the U.S. Authority to regulate the sale, purchase, barter, exchange, advertisement, giving, or receiving of any noxious weed.	"Noxious weed" is defined as "any living stage (including but not limited to seeds and reproductive parts) of any parasitic or other plant of a kind or subdivision of a kind, which is of foreign origin, is new to or not widely prevalent in the U.S., and can directly or indirectly injure crops, other useful plants, livestock, or poultry or other interests of agriculture including irrigation or navigation or the fish and wildlife resources of the United States or the public health."	USDA-APHIS	No action may be taken to regulate interstate movement unless a State also takes a cooperative action to erradicate the noxious weed in its State.	Authority to seize, quarantine, treat, destroy or otherwise dispose of any product or article of any character whatsoever, or means of conveyance, which is moving into or through the U.S. or interstate and which is believed to be infested by any noxious weed, or contains any noxious weed, or which was infested or contained any noxious weed at the time of movement.
TSCA Section 13	Substance imported into the US must be in compliance with TSCA.	TSCA "chemical substances"	EPA, USDA-APHIS Treasury Dept.		Mandatory requirement.
Regulations: 40 CFR 707 19 CFR 12, 127	Section 13 import provisions; requires companies importing "chemical substances" to certify compliance with TSCA		EPA, USDA-APHIS Treasury Dept.	Federal Plant Pest Act, Federal Noxious Weed Act, "Exotic Organisms" Executive Order 11987 also regulate imports	Rules were issued by Treasury Department and EPA.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
III. EXPORT CONTROLS	Technical Data				
Export Administration Act (540 USC 2401, et seq.) Regulations: 15 CFR 368-399	All non-public technical data exported to Eastern Bloc Countries, Libya, Cuba, N. Korea, Afghanistan, Kampuchea, and Vietnam requires a validated license.	Technical data related to all biotechnologies	Dept. of Commerce-Int'l Trade Admin. (DOC-ITA)		Statute provides discretionary authority to restrict technical data for three reasons: a) Foreign Policy b) National Security c) Short Supply Although authority to administer the EAA terminated, it was extended indefinitely by Executive Order 12370 of March 30, 1984.
	Commodities				
	Listed products cannot be exported to any country except Canada without a validated license from the Department of Commerce.	Bacteria, fungi, protozoa, virus, human and animal vaccines, human and animal peptides and proteins, rDNA, nucleotides and side antibiotics and diagnostics, amino acids, vitamins, enzymes, pesticides, herbicides and seeds	DOC-ITA		Restrictions generally apply to Soviet Bloc countries and those countries with which we do not have diplomatic relations.
IV. RESEARCH AND INFORMATION GATHERING					
A. Research					
PHS Act Section 301 (42 USC 241)	Biomedical research authority, both intramural and extramural research	Basic and applied research related to foods, drugs, biologics, new surgical techniques, chemicals as carcinogens (NIEHS, NTP, NCTR), medical devices.	HHS-NIH, ADAMHA, CDC, FDA		HHS has many other research authorities for specific diseases, but Section 301 is sufficient to do biomedical research related to human health.
Organic Act of 1962 (7 USC 2201-2204)	Agricultural research authority, both intramural and extramural	Plants and animals	USDA-ARS		USDA also has many authorities for research, just as NIH, including: Domestic Animals, Dairy Industry, Aboretum, Forest and Rangeland, Cotton and Nutrition

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Organic Act of 1944 Section 101(d) (7 USC 430)	Authority to purchase and test samples of all tuberculin, serums, antitoxins, or analogous products, of foreign or domestic manufacture, which are sold in the U.S. for the detection, prevention, treatment or cure of diseases of domestic animals.		USDA-ARS		
TSCA, FIFRA, RCRA, Clean Water Act	Environmental research authority, both intramural and extramural	TSCA "chemical substances," pesticides, hazardous wastes, air and water pollutants	EPA		
B. Information Gathering					
Federal Seed Act (7 USC 1551-1611) Regulations: 7 CFR 201 et seq.	Requires specific recordkeeping on labeling, importation and interstate movement of seeds.	Agricultural and vegetable seeds	USDA-APHIS		The term "treated" means given an application of a substances or subjected to a process designed to reduce, control, or repel disease organisms, insects, or other pests which attack seeds or seedlings growing therefrom.
TSCA Section 4	Authorizes EPA to require manufacturers by rule to test specific "chemical substances"	TSCA "chemical substances"	EPA		Discretionary authority; could be be used to require testing of specific products developed through genetic engineering (both organisms and chemicals produced by organisms); could be used to support activities of other agencies (e.g., OSHA, CPSC). No regulations affecting biotechnology now in effect.
TSCA Section 8(a)	Authorizes EPA to require manufacturers and processors to submit information on a product's identity, exposure, available health and safety data, etc.		EPA		Discretionary authority invoked by rule; can be used to support other agencies; small businesses generally exempt from reporting. No biotechnology rule now in effect.
TSCA Section 8(d)	Authorizes EPA to require submission of health and safety studies on products subject to TSCA.		EPA		Discretionary authority invoked by rule; no biotechnlogy rules now in effect.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
TSCA Section 8(e)	Requires submission of information on substantial risks from "chemical substances."	TSCA chemicals	EPA		Mandatory requirement if substance subject to TSCA and information shows substantial risk.
Guideline: 43 FR 11110 (1978)	Policy for submitting information under Sec. 8(e)	TSCA chemicals	EPA		Mandatory requirement if substance subject to TSCA.
FIFRA Section 6(a)(2)	Continuing obligation for registrants to supply data	All registered products	EPA		After registration, registrants must report additional information on unreasonable adverse effects of pesticide. The "interpretation" is undergoing revision currently.
Guideline: Interpretation of Requirements on Registrants by Section 6(a)(2), August 23, 1978 (43 FR 37611 and 44 FR 40716)					
FIFRA Section 3(c)(2)(B)	Authorizes EPA to request additional data in support of registration	All registered products	EPA		After registration, EPA may require additional data from registrants in order to maintain registrations.
V. PATENTS					
Patent and Trademark Laws (35 USC 1 et seq.)	Patent process	All products and devices	DOC-Patent and Trademark Office	Patent for new drugs issued well before FDA premarket approval. Important: Government research institutions can offer Institutional Patent Agreements with universities for 5 to 8 years after market appproval under PL 96-517.	
Regulations: 37 CFR					
Plant Variety Protection Act (7 USC 2321 et seq.)	Granting of patents for sexually reproduced varieties of plants.	New varieties of sexually reproduced plants	USDA-Agriculture Marketing Service (AMS)		
Regulations: 7 CFR 180					
Judicial Decisions:					
Diamond v. Chakrabarty 447 US 303 (1980)	Supreme Court held that genetically engineered bacterium was patentable.			Court cited NIH guidelines in decision as addressing the problems of genetic engineering.	

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
VI. AIR AND WATER EMISSIONS					
Clean Air Act (42 USC 7401-7642)	Requires emission standards to be set for hazardous air pollutants where there is no applicable ambient air quality standard.		EPA		Discretionary authority; no genetically engineered organisms now included, but could be set for biotechnology products if concern warranted.
Regulations: 40 CFR 61	Sets national emission standards for specific hazardous air pollutants		EPA		
Clean Water Act (33 USC 1251-1376)	Pollutant discharges without National Pollutant Discharge Elimination System (NPDES) permit unlawful. Pollutant defined to include living organisms; requires EPA to establish effluent limitations for point sources.	Genetically engineered organisms or byproducts that are discharged into the waters of the U.S.	EPA, States	States establish water quality standards. States or EPA issue permits which incorporate technology-based limits and water quality-based limits.	Regulations developed for drug manufacturers, pesticide manufacturers and hospital. (See 40 CFR 401-469, below.)
Regulations:					
40 CFR 122, 125	NPDES permit program		EPA, States		Implemented by States and EPA. Source employing biotechnology will be required to adhere to permit restrictions.
40 CFR 120, 121	State water quality standards, State certification requirements		EPA, States		
40 CFR 401-469	Effluent guidelines and standards for categories of point sources		EPA, States		Specific biotechnology category not issued, but some categories could involve biotechnology products (e.g., part 439, pharmaceutical manufacturing; part 460, hospitals; and part 455, pesticides).
Safe Drinking Water Act (SDWA) (42 USC 300f et seq.)					
Section 300g-1	Authorizes promulgation of maximum containment levels for drinking water from public water systems.	Any physical, chemical, biological or radiological substances or matter in drinking water	EPA		No genetically engineered biological substances now included. Could be regulated if it presents a known or anticipated adverse effect on health.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Section 300h-1	Requires state programs to regulate any injection of any substance into a well; provides for minimum regulatory standards for such programs in order to prevent underground injection that endangers drinking water.	Any substance injected into the subsurface through a well	EPA		See 40 CFR Parts 144, 145, and 146. If disposed of by deep well injection, subject to stringent requirements for Class I wells regarding well construction, operation, monitoring, and reporting; if not a deep well, then would be Class V, subject only to a general prohibition on endangerment to drinking water sources.
VII. REQUIREMENTS FOR FEDERAL AGENCIES					
National Environmental Policy Act (NEPA) Section 102(2)(C) (42 USC 4321-4361) Regulations: 40 CFR 1500-1508	Requires all agencies to prepare environmental impact statements on "major Federal actions significantly affecting the environment."		All Federal Agencies	Administered by Council on Environmental Quality	Applies only to Federal actions (e.g., federally funded projects or premarket approval). Each agency develops its own guidelines or regulations under this Act. Procedural requirements generally held inapplicable to EPA actions.
Endangered Species Act of 1973, as amended, Section F (16 USC 1536) Regulations: 50 CFR 402	Requires Federal agencies to insure that their activities or programs will not jeopardize the continued existence of a listed species.	All species of fish, wildlife and plants listed pursuant to the Endangered Species Act.	All Fed. agencies	Consultation required with the U.S. Dept. of the Interior or the National Marine Fisheries Service.	
Executive Order 11987 "Exotic Species"	Orders Executive Agencies (to extent permitted by law) to restrict the imporation into the U.S., and introduction of exotic specimens into the natural ecosystems. Exempts from provisions of Executive Order 11987 the introduction or exportation of exotic species when USDA or USDI finds that the introduction or exportation will not have an "adverse effect on natural ecosystems."	"Exotic Species" is defined to mean all species of plants and animals not naturally occurring, either presently or historically, in any ecosystem of the U.S.	All Fed. agencies		Secretary of the Interior in consultation with Secretary of Agriculture is required to develop and implement by rule or regulation a system to standardize and simplify the requirements, procedures, and other activities appropriate for implementing the provisions of Executive Order 11987. No rule has been developed.

AUTHORITY OR GUIDELINE	DESCRIPTION	AFFECTED PRODUCTS OR PROCESSES	AFFECTED AGENCIES	CROSS-REFERENCES	NOTES
Judicial Decisions:					
Foundation on Economic Trends v. Heckler, 14 ELR 20467 (D.D.C. 5/16/84)	Preliminary injunction prohibiting NIH approval of environmental release of organisms containing rDNA pending final judgment by the court regarding compliance with NEPA.	INA-minus bacteria and all future submissions for NIH review.	HHS-NIH		Decision applies only to requests from institutions receiving NIH rDNA funding.

BILLING CODE 6560-50-C

FOOD AND DRUG ADMINISTRATION

Statement of Policy for Regulating Biotechnology Products

AGENCY: Food and Drug Administration.

ACTION: Statement of Policy for Regulating Biotechnology Products.

SUMMARY: This notice describes the regulatory policy of the Food and Drug Administration applicable to biotechnology in general. Public comment is requested on scientific and policy issues raised by this notice.

ADDRESS: Written comments should be submitted to: Docket #84N–0431, Dockets Management Branch, Food and Drug Administration (HFA–305), Room 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION, CONTACT: Dr. Mary Ann Danello, Food and Drug Administration (HF–5), Room 14–90, 5600 Fishers Lane, Rockville, MD 20857. Telephone: (301) 443–4650.

Introduction

A small but important and expanding fraction of the products the Food and Drug Administration (FDA) regulates represents the fruits of new technological achievements. These achievements are in areas as diverse as polymer chemistry, molecular biology, and micro-miniaturization. It is also noteworthy that technological advancement in a given area may give rise to very diverse product classes, some or all of which may be under FDA's regulatory jurisdiction. For example, new developments in recombinant DNA research can yield products as divergent as food additives, drugs, biologics, and medical devices.

Although there are no statutory provisions or regulations that address biotechnology directly, the laws and regulations under which the Agency operates place the burden of proof of safety as well as effectiveness of products on the manufacturer, except for traditional foods and cosmetics. The adminsitrative review of products using biotechnology is based on the intended use of each product on a case-by-case basis.

This notice describes the regulatory policy of the FDA applicable to biotechnology in general. The manner in which regulations for biotechnology are implemented in the United States could have a direct impact on the competitiveness of U.S. producers in both domestic and world markets. Inconsistent or duplicative domestic regulation will put U.S. producers at a competitive disadvantage. In addition, certification systems which favor domestic products, if adopted by our trading partners, could create substantial nontariff barriers to trade and block market access. Therefore during the development of the U.S. regulatory procedures for biotechnology products, attention is being paid to the need for achieving consistency in national regulation and international harmonization. With respect to international harmonization the U.S. is seeking to promote scientific cooperation, mutual understanding of regulatory approaches international agreement on a range of common technical problems such as the development of consistent test guidelines, laboratory practices and principles for assessing potential risks. In achieving national consistency and international harmonization, regulatory decisions can be made in a socially responsible manner, protecting human health and the environment, while allowing U.S. producers to remain competitive.

The Agency possesses extensive experience with the administrative and regulatory regimens described as applied to the products of biotechnological processes, new and old, and proposes no new procedures or requirements for regulated industry or individuals. Public comment is requested on scientific and regulatory policy issues raised by this notice.

The marketing of new drugs and biologics for human use, and new animal drugs, requires prior approval of an appropriate new drug application (NDA), license, or new animal drug application (NADA). For new medical devices, including diagnostic devices for human use either a premarket approval application or reclassification petition is required. If the device is determined to be equivalent to an already marketed device, a premarket notification under section 510(k) of the Federal Food, Drug, and Cosmetic Act (the act) is required. For food products, section 409 of the act requires FDA preclearance of food additives including those prepared using biotechnology. Section 706 of the act requires preclearance of color additives. The implementing regulations for food and color additive petitions and for affirming generally recognized as safe (GRAS) food substances are sufficiently comprehensive to apply to those involving new biotechnology.

Genetic manipulations of plants or animals may enter FDA's jurisdiction in other ways; for example, the introduction into a plant of a gene coding for a pesticide or growth factor may constitute adulteration of the foodstuff derived from the plant, or the use of a new microorganism found in a food such as yogurt could be considered a food additive. Such situations will be evaluated case-by-case, and with cooperation with the U.S. Department of Agriculture (USDA), where appropriate.

The Regulatory Process

Congress has provided FDA authority under the act and the Public Health Service (PHS) Act to regulate products regardless of how they are manufactured.

General Requirements for Human Drugs and Biologics

A new drug is, in general terms, a drug not generally recognized by qualified scientific experts as safe and effective for the proposed use. New drugs may not be marketed unless they have been approved as safe and effective, and clinical investigations on human subjects by qualified experts are a prerequisite for determination of safety and effectiveness. Sponsors of investigations of new drugs or new drug uses of approved drugs file an Investigational New Drug Application (IND) to conduct clinical investigations on human subjects. The IND must contain information needed to demonstrate the safety of proceeding to test the drug in human subjects, including, for example, drug composition, manufacturing and controls data, results of animal testing, training and experience of investigators, and a plan for clinical investigation. In addition, assurance of informed consent and protection of the rights and safety of human subjects is required. FDA evaluates IND submissions and reviews ongoing clinical investigations. Significant changes in the conditions of the study, including changes in study design, drug manufacture or formulation, or proposals for additional studies, must be submitted to FDA as amendment to the IND.

FDA approval of a New Drug Application (NDA) or an abbreviated New Drug Application (ANDA) is required before the new drug can be marketed. The NDA must contain:

- Full reports of investigations, including the results of clinical investigations, that show whether or not the drug is safe and effective;
- A list of components of the drug and a statement of the drug's quantitative composition;
- A description of the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug;
- Samples of the drug and drug components as may be required; and
- Specimens of the proposed labeling.

NDA holders who intend to market an approved drug under conditions other than those approved in the NDA must submit a supplemental NDA containing clinical evidence of the drug's safety and effectiveness for the added indications. Extensive changes such as a changed formula, manufacturing process, or method of testing differing from the conditions of approval outlined in the NDA may also require additional clinical testing.

Section 351 of the PHS Act defines a "biological product" as "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product * * * applicable to the prevention, treatment, or cure of diseases or injuries of man * * *." Biologics are regulated similarly to new drugs during the IND phase; approval for marketing is granted by license, which is only issued upon demonstration that both the manufacturing establishment and the product meet standards designed to ensure safety, purity, potency, and efficacy. All biologics are subject to general provisions in the regulations that assure potency, general safety, sterility, and purity. In addition, specific tests and standards are established for particular products. To obtain a license, the manufacturer must submit information demonstrating that the manufacturing facility and the product meet FDA standards, and the facility must pass a prelicensing inspection. Licensed products are subject to specific requirements for lot release by FDA.

Manufacturers of new drugs and biologics must operate in conformance with current good manufacturing practice (CGMP) regulations, which address: adequately equipped manufacturing facilities; adequately trained personnel; stringent control over the manufacturing process; and appropriate finished product examination. CGMP's are designed to protect the integrity and purity of the product. Approval of the product application is also approval of the sponsor's process techniques.

General Requirements for Animal Food Additives and Drugs

Animal food additives and drugs are subject to similar mandatory requirements of the act as the like products for use in humans. Animal biologics, however, are regulated by the U.S. Department of Agriculture under the authority of the Virus-Serum-Toxin Act of 1913. Uncertainties as to whether a product fits the definition of a drug or biological drug are decided by a standing committee comprised of representatives from USDA and FDA.

Application for approval must go through the Investigational New Animal Drug (INAD) and New Animal Drug Application (NADA) process similar to that required for human drugs, as discussed earlier. The regulations pertaining to INAD's do not require that the Agency approve clinical investigations, only that the food being marketed from treated food-producing animals be safe for human consumption. The data must be specific for each animal species for which the drug is intended. For NADA approval, it must be shown that those drugs which are intended for use in food-producing animals and used in accordance with approved label directions, do not accumulate as unsafe residues in the edible tissues of the animal at the time of slaughter. Moreover, the manufacturer must submit acceptable methods for recovery and detection of any drug residue in edible tissues. To further insure drug quality, animal drugs, including medicated feeds, must be manufactured in conformance with CGMP's.

Substances that are used in animal feeds, other than drugs, and that are produced by recombinant DNA technology, are considered to be food additives and require approval of a food additive petition (FAP). Other products of new biotechnology may also be considered to be food additives, requiring an FAP. Animal drugs or food additives produced by recombinant DNA technology must be the subject of approval even if the active substance is shown to be identical or similar to the active substance in approved products produced by conventional methods.

General Requirements for Medical Devices

Medical devices for human use are regulated by requirements of the act as amended by the Medical Device Amendments of 1976. In general terms, a device is defined in the act as any health care product that does not achieve any of its principal intended purposes by chemical action in or on the body or by being metabolized. Devices include diagnostic aids such as reagents, antibiotic sensitivity discs, and test kits for *in vitro* diagnosis of disease. Veterinary medical devices are subject to the act but are not subject to preclearance requirements.

Regulations promulgated under the Medical Device Amendments control introduction of medical devices into commerce. In May 1976 when these device amendments were enacted, expert advisory committees recommended classifications for all medical devices of the types marketed at that time. The law segregates medical devices into three classes:

Class I devices are subject to the minimum level of control; general controls include the CGMP's.

Class II devices have been declared to require performance standards to assure their safety and/or effectiveness. They must also meet the controls of class I.

Class III devices require formal FDA approval of a Premarket Approval Application (PMAA) for each make and model of the device to assure its safety and effectiveness. The controls of class I are also required.

Before a manufacturer may introduce into commerce any medical device not previously marketed, the manufacturer must formally declare that intent to FDA and proceed along one of two legal avenues. The manufacturer can file a premarket notification to FDA seeking a determination that the device is substantially equivalent to a preamendment device and proceed to market the device subject to whatever controls apply to the older versions of the device depending on its classification. This is the so-called "510(k)" process, which takes its name from a paragraph in the act.

A new device—that is, one not substantially equivalent to a preenactment device—is automatically a class III device requiring FDA approval of a PMAA unless FDA reclassifies it into class I or class II. In the premarket approval process, the manufacturer must establish that the device is safe and effective. This is typically accomplished by scientific analysis by the Agency of product performance and data from clinical trials, submitted by the manufacturer in the PMAA.

For a "significant risk device," as defined in FDA's regulations, the sponsor must submit an application to FDA for approval to conduct the investigation. This application is known as the Investigational Device Exemption (IDE). When the manufacturer believes there are sufficient data to establish the safety and effectiveness of its device, the manufacturer may file a premarket approval application, or PMAA. The law requires that FDA act on such an application within 180 days.

Regulation of Specific Products

Within the framework of FDA's statutes and regulations, strategies have been developed for the evaluation of various kinds of "biotechnological" or "genetically engineered" products, as well as for other products. These

strategies are product-specific rather than technology-specific. For example, review of the production of human viral vaccines routinely involves a number of considerations including the purity of the media and the serum used to grow the cell substrate, the nature of the cell substrate, and the characterization of the virus. In the case of a live viral vaccine, the final product is biologically active and is intended to replicate in the recipient. Therefore, the composition, concentration, subtype, immunogenicity, reactivity, and nonpathogenicity of the vaccine preparation are all considerations in the final review, whatever the techniques employed in "engineering" the virus.

Scientific considerations may dictate areas of generic concerns or the use of certain tests for specific situations. For example, a hepatitis B vaccine produced in yeast (via recombinant DNA techniques) would be monitored for yeast cell contaminants, while distinctly different contaminants would be of concern in a similar vaccine produced from the plasma of infected patients.

In order to provide guidance to current or prospective manufacturers of drugs and biological products, the FDA has developed a series of documents describing points that manufacturers might wish to consider in the production of interferon, monoclonal antibodies, and products of recombinant DNA technology, as well as in the use of new cell substrates. These documents, called "Points to Consider . . .", are available from the Agency upon request.

Administrative jurisdiction within FDA's various organizational units are the same for a given product, whatever the processes employed in its production.

Nucleic acids used for human gene therapy trials will be subject to the same requirements as other biological drugs. It is possible that there will be some redundancy between the scientific reviews of these products performed by the National Institutes of Health and FDA.

Obligations Under the National Environmental Policy Act

All premarket approvals of FDA-regulated products are subject to the requirements of the National Environmental Policy Act (NEPA) as defined by the Council on Environmental Quality's regulations (40 CFR Parts 1500–1508) and as further described by FDA's NEPA-implementing procedures (21 CFR Part 25, revision proposed December 11, 1979; 44 FR 71742–71752). For new products or major new uses for existing products, these procedures ordinarily require the preparation of an environmental assessment. An environmental impact statement is required if manufacture, use, or disposal of the product is anticipated to cause significant environmental impacts.

Scientific Issues Surrounding Specific Products

There are some scientific issues raised by specific products manufactured with recombinant DNA technology. First, the molecular structure of some products is different from that of the active molecule in nature. For example, the "human growth hormone" from recombinant microorganisms has an extra amino acid, an amino-terminal methionine; hence, it is an analogue of the native hormone. Such differences may affect the drug's activity or immunogenicity and these considerations, among others, may affect the amount of clinical testing required. However, FDA possesses exensive experience with evaluation of analogues of native human polypeptides, a number of which have been approved for marketing.

Second, appoval of the product application for pharmaceuticals is also approval of the sponsor's processing techniques, and FDA must determine whether the quality assurance within the manufacturing process is adequate to detect deviations that might occur, such as the occurrence of mutations in the coding sequence of the cloned gene during fermentation. Such mutations could, in theory, give rise to a subpopulation of molecules with an anomalous primary structure and altered activity. This is a potential problem inherent in the production of polypeptides in any fermentation process. One way FDA has dealt with these situations in existing IND's is to require batch-by-batch testing with appropriate techniques to ensure that the active drug substance is homogenous and has the correct identity.

Summary

FDA's administrative review of products, including those that employ specialized biotechnological techniques such as recombinant DNA in their manufacture, is based on the intended use of product on a case-by-case basis. Although scientific considerations may dictate areas of generic concerns for certain techniques, e.g., the possibility of contamination with adventitious agents or oncogenes when cultured mammalian cells are the source of a drug, the use of a given biotechnological technique does not require a different administrative process. Regulation by FDA must be based on the rational and scientific evaluation of products, and not on *a priori* assumptions about certain processes.

FDA Approved Drugs and Biologics of New Biotechnology (Recombinant DNA and Hybridoma Techniques)

Hormones
- Human insulin (*)

In Vitro Diagnostic Products
- Anti-Human serum (**)
- Anti-Human serum anti-C3d (**)
- [I^{125}]Antibody to Hepatitis B Surface Antigen (**)

ENVIRONMENTAL PROTECTION AGENCY

Proposed Policy Regarding Certain Microbial Products

SUMMARY: This notice describes how EPA plans to address certain microbial products of biotechnology under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA). The notice outlines EPA's plan for review of nonindigenous and genetically engineered microbial pesticides under FIFRA, and EPA's interpretation of the new chemical premanufacture notification (PMN) provisons of TSCA section 5 for new genetically engineered microorganisms used for commercial purposes. Public comment is requested on scientific and policy issues raised by this notice.

ADDRESS: Because some comments may contain confidential business information, all comments on the EPA portion of this notice should be identified by Docket Number OPTS–00049 and addressed to: Document Control Officer (TS–793), Office of Toxic Substances, Environmental Protection Agency, Rm. E–409, 401 M St., SW., Washington, D.C. 20460.

Information submitted as comments on the EPA portion of this notice may be claimed confidential by marking any part or all of that information as "Confidential Business Information." Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR Part 2. A sanitized copy of any material containing Confidential Business Information must be provided by the submitter for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice.

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*Produced by recombinant DNA technique.
**Produced by hybridoma technique.

Comments received on ths notice, except those containing confidential business information, will be available for review and copying from 8 a.m. to 4 p.m. Monday through Friday, except legal holidays, in the TSCA Public Information Office, Rm. E–107 at the address given above.

FOR FURTHER INFORMATION CONTACT: For general information including copies of the following EPA portion of this notice and related materials: Edward A. Klein, Director, TSCA Assistance Office (TS–799), Office of Toxic Substances, Environmental Protection Agency, Rm. E–543, 401 M St., SW., Washington, D.C. 20460, Toll-free: (800–424–9065), In Washington, D.C.: (202–554–1404, Outside the USA: (Operator–202–554–1404).

For technical information regarding the FIFRA sections of the EPA proposed policy: Frederick S. Betz, Hazard Evaluation Division (TS–769c), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, D.C. 20460. Office location and telephone number: Rm. 1123, Crystal Mall #2, 1921 Jefferson Davis Highway, Arlington, VA 22202, (703–557–9307).

For technical information regarding the FIFRA sections of the EPA proposed policy: Anne K. Hollander, Office of Toxic Substances (TS–794), Environmental Protection Agency, Rm. E–511, 401 M St., SW., Washington, D.C. 20460, (202–382–3852).

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I. Introduction

A. Scope of This Notice

The Federal Insecticide, Fungicide, and Rodenticide Act provides EPA authority over pesticidal products, including the authority to review and register new pesticides; the Toxic Substances Control Act provides EPA authority over non-pesticidal, non-food, and non-drug products, and requires EPA to review "new chemical substances" before commercial manufacture. These statutes will apply to certain commercial products of biotechnology, just as they already apply to chemical and biological products developed by more conventional methods.

This notice describes how EPA plans to address certain microbial products under FIFRA and TSCA. It explains the scope of coverage and procedures for review under both statutes, and it highlights the similarities and differences between treatment or nonindigenous and genetically engineered microbial substances and other substances. In doing so, the following questions are addressed:

1. Which products of biotechnology may be subject to review under FIFRA or TSCA?

2. How does the Office of Pesticides and Toxic Substances (OPTS) propose to use its authority under FIFRA and TSCA to review products of biotechnology?

3. Should the procedures used under FIFRA and TSCA to review conventional products be changed in the review of nonindigenous and genetically engineered microbial products used for environmental and consumer applications?

4. What data requirements should be applied to microbial products under FIFRA and TSCA?

This notice primarily addresses microorganisms used as commercial products, emphasizing those areas in which EPA believes its oversight will contribute most to human or environmental safety, and where the application of FIFRA and TSCA are most appropriate. Chemical products derived from microbes, plants and animals will also be discussed briefly in the respective units pertaining to FIFRA and TSCA.

Although the microorganisms discussed in this notice include naturally occurring, indigenous microbes as well as nonindigenous and genetically engineered microbes, emphasis has been placed on the latter groups. "Nonindigenous" or "exotic" microbes are natually occurring microorganisms placed in environments where they are not native. "Genetically engineered" organisms are defined in the glossary to this notice.

In the approach discussed in this notice, nonindigenous and genetically engineered microbial pesticides may, on a case-by-case basis, be subject to greater data requirements under FIFRA than other microbial pesticides. Genetically engineered microorganisms used for non-drug, non-food, or non-pesticidal purposes (such as pollution control or enhanced oil recovery) would be subject to premanufacture review under TSCA.

Proposed approaches under FIFRA and TSCA are discussed in detail in Units II and III of this notice. Unit IV identifies intra-agency, interagency, and international activities, and references are found in Unit V.

B. Common Issues Under FIFRA and TSCA

FIFRA and TSCA provide authority to review certain products of biotechnology before commercial manufacture, including microbial products used in environmental and

consumer applications. These two statutes, both of which are administered by EPA through OPTS, have numerous similarities, even though they entail different responsibilities and apply to different classes of products. One goal of the two OPTS offices responsible for administering these statutes—the Office of Pesticide Programs (OPP) and the Office of Toxic Substances (OTS)—is to develop a consistent program within the constraints of the two statutes.

In developing this program, OPP and OTS are addressing a number of common issues. These issues are identified here and discussed more fully in subsequent units of this notice.

1. *Risk assessment information needs.* A major common issue is the need to determine what information is necessary for assessing the risks posed by nonindigenous and genetically engineered microorganisms. Although OPP has experience with regulating naturally occurring microbial pesticides, there is concern about potential human or environmental risks specific to nonindigenous and engineered microbes. As a result, the type and amount of information needed to assess any special risks of these microbial products will be determined on a case-by-case basis, as discussed in Units II.F and III.E.

(2) *Direct release of microorganisms to the environment.* A second common issue is at what stage EPA should review certain microbial products before any direct release to the environment, such as small-scale field testing. The Agency believes that review of small-scale field testing of nonindigenous and genetically engineered products is necessary in order to provide adequate protection to human health and the environment. Comments are requested on this issue, which is discussed in Units II.F and III.B.5.

3. *Plants and animals.* A third common issue is whether it is necessary or appropriate for OPTS to address genetically engineered plants and animals. Currently, OPP has exempted plants and animals used as pesticides from review under FIFRA because they are addressed by other Federal agencies. EPA also believes that other statutes and regulations are likely to be more appropriate for regulating engineered plants and animals used for purposes potentially subject to TSCA (e.g., production of fiber or lumber). Therefore, EPA does not propose that plants and animals be subject to TSCA review. This issue is discussed in Units II.B and III.A.3 of the notice.

4. *Coordination with other Federal agencies.* A fourth common goal of OTS and OPP is to coordinate with other Federal agencies with interests in biotechnology, including the U.S. Department of Agriculture (USDA), the Occupational Health and Safety Administration (OSHA), the Department of Health and Human Services (HHS), the Department of Commerce, and others. Such coordination can eliminate regulatory overlaps, achieve a clear delineation of each agency's responsibility, and insure a consistent Federal approach in coordinating Federal research sharing information on risk assessment methods for products of biotechnology.

Coordination with the USDA is particularly important to the EPA because USDA has jurisdiction over some of the same organisms which EPA regulates. The fact that a plant-associated microorganism may be subject to an EPA law does not exempt it from any applicable statutes administered by the USDA. For example, all microbes which are plant pathogens are subject to the USDA Plant Pest Act, and all microbes used as pesticides are subject to FIFRA. Therefore if a microbe is a plant pathogen and a pesticide, it is subject to both USDA and EPA laws. Similarly, microbes which are sold in conjunction with seeds fall under various seed certification programs, even though they may also be subject to FIFRA or TSCA because of their intended uses.

EPA and USDA will work cooperatively and simultaneously in the evaluation of genetically engineered products which fall under the jurisdiction of both agencies. For further information on the applicable authorities of EPA and USDA, refer to the EPA policy statements on TSCA and FIFRA, and to the USDA Statement of Policy elsewhere in this notice.

Interagency coordination is discussed further in Unit IV. B.

5. *Need for a balanced approach among safety, regulation, and innovation.* The potential benefits of biotechnology are enormous, both to consumers who will enjoy new, enhanced, or less expensive products, and to the economy as a whole. Despite this potential, biotechnology is still in its commercial infancy, and innovation and commercial development in the field is extremely sensitive to regulatory uncertainty.

Both FIFRA and TSCA are risk-balancing statutes, drafted by the Congress to require a balance between the restrictions and higher costs created by a regulation and the lower risks to public health and the environment. Under both statutes, therefore, EPA plans to develop a policy for biotechnology that addresses this balance, is supported by sound science, and incorporates new information as it becomes available.

II. Applicability of FIFRA To Nonindigenous and Genetically Engineered Microbial Products

A. General Scope of FIFRA

FIFRA establishes the Agency's authority over the distribution and use of pesticide products. Before the Agency can register a pesticide, FIFRA requires the Agency to have sufficient data to determine that the pesticide, when used in accordance with widespread and commonly recognized practice, will not cause (or significantly increase the risk of) unreasonable adverse effects to humans or the environment (see section 3(c)(5) and (7) of FIFRA). Such data are also specifically required in the regulations promulgated pursuant to FIFRA at 40 CFR 162.8 and 162.18–2.

The Agency has issued a final regulation, 40 CFR Part 158, published in the **Federal Register** of October 24, 1984 (40 CFR 42856), specifying the kinds of data and information that must be submitted to EPA to support the registration of each pesticide under FIFRA. The Agency has also published the Pesticide Assessment Guidelines for microbial pesticides. This is an advisory document which is available through the National Technical Information Service (NTIS). The guidelines specify the standards for conducting acceptable tests, and provide guidance on evaluation and reporting of data, further guidance on when data are required, and examples of recommended testing protocols. The Agency must conduct a complete evaluation and review of the data submitted to support a pesticide registration prior to the Agency's determination of the registerability of the product with respect to the criteria set forth in 40 CFR 162.7(d) and (e) and 162.18–4.

More recently, the Agency has issued a statement of interim policy on small-scale field testing of nonindigenous and genetically engineered microbial pesticides. This policy, published in the **Federal Register** of October 17, 1984 (49 FR 40659), is discussed in detail in Unit II.F. of this notice.

B. Scope of This Unit

This unit of the notice addresses those nonindigenous and genetically engineered microorganisms which are considered pesticides under FIFRA section 2(u) and which are defined as biological control agents. 40 CFR 162.5(c)(4) currently specifies that

microorganisms, when used as pesticides, are regulated under FIFRA.

As indicated in Unit I.B.4 above, the Agency has determined that certain non-microbial living organisms which fall within the definition of biological control agents are already addressed by other agencies, specifically USDA and the Department of the Interior (DOI). Examples of these biological control agents are vertebrates, insect predators, nematodes, and macroscopic parasites. Therefore, pursuant to section 25(b) of FIFRA and 40 CFR 162.5(c)(4), these non-microbial biological control agents have been exempted from regulation under FIFRA. However, if EPA, in cooperation with other agencies, determines that certain biological control agents exempted by § 162.5(c)(4) are not being adequately regulated, these organisms would be referred to the attention of the appropriate agency, or would be added to the exceptions in § 162.5(c)(4) by amendment. In the latter case, those organisms would no longer be considered exempt from the provisions of FIFRA.

This unit of the notice does not address any chemical pesticide product, or chemical byproduct produced by microorganisms. Such chemicals are covered under current pesticide regulations, registration procedures, data requirements, and testing guidelines (see 40 CFR Parts 158 through 180; and Subdivisions D through O of the Pesticide Assessment Guidelines).

C. Background/History

1. *Past activities related to microbial pesticides.* The first microbial pesticide (*Bacillus popilliae*) was registered in 1948. This pesticide was made of naturally occurring bacteria. However, it was not until the late 1960s and early 1970s that interest in microbial pesticides began to increase. As of 1983, there were 14 microbial pesticides used in about 100 separate products registered for use in agriculture, forestry, mosquito control, and homeowner situations.

In recognition of the growing interest and concern about microbial pesticides, the Agency began (in 1974) sponsoring a variety of workshops, symposia, and panel discussions aimed at identifying the relevant safety concerns for microbial pesticides. As early as 1978, at an EPA symposium title "Viral Pesticides: Present Knowledge and Potential Effect on Public and Environmental Health," the need for sensitive identification and detection methods as well as quality assurance provisions were clearly identified. In the same year, intramural and extramural research on developing methods for molecular characterization and genetic mapping of entromopathogenic viruses was initiated.

OPP issued a Policy Statement on Biorational Pesticides which was published in the Federal Register of May 14, 1979, (44 FR 23994). In it, OPP recognized microbial pesticides as distinct from conventional chemical pesticides, and committed OPP to developing appropriate testing guidelines within 2 years. In 1979, OPP commissioned an American Institute of Biological Sciences' expert panel to develop a "Human Hazard Evaluation Scheme for Biorational Pesticides." The final report of this expert panel formed the basis for the human toxicology unit of the testing guidelines for microbial pesticides. The next year, OPP formally requested the EPA Offices of Research and Development (ORD) to develop and validate test methods for evaluating the safety of microbial pesticides to humans and the environment.

OPP completed draft testing guidelines for Microbial and Biochemical Pesticides in 1980. The biochemical pest control agents include pheromones, hormones, natural insect and plant growth regulators, and enzymes, and the microbial pest control agents include bacteria, viruses, fungi, and protozoa. After review by the FIFRA Scientific Advisory Panel (SAP) and public comment, these guidelines were published as Subdivision M of the Pesticides Assessment Guidelines through the NTIS in 1983.

The microbial pesticide portion of the Subdivision M guidelines applies to both naturally occurring and genetically modified microbial pesticides. However, the specific data that would be required for the registration of genetically modified microorganisms would be determined on a case-by-case basis by EPA. This approach was supported in the final report (September 1983) of the Biorational Workshop (September 15–17, 1982) that was sponsored by ORD at the request of OPP. The Workshop was designed primarily to evaluate and review Subdivision M and the status of testing for the safety of microbial and biochemical pesticides to nontarget, nonhuman organisms; however, safety concerns relating to all nontargets, including humans were addressed. The workshop final report made a number of recommendations for improving the guidelines, but concurred with the philosophy and with the tiered testing scheme, and generally agreed with the safety testing proposed for registering naturally occurring microorganisms. Concerning genetically modified microbial pesticides, the report stated in part that

> . . . each situation [application for registration] will require a case-by-case determination of test requirements for registration. . . The consensus was that any undesirable effects of genetically engineered agents could be detected in Tier 1 level testing or any specially designed tests appropriate for the agent to be evaluated.

The Data Requirements for Pesticide Registration, 40 CFR Part 158, contain data requirements for microbial pesticides (including genetically engineered microbial pesticides) at § 158.170. These data requirements were previously reviewed by the FIFRA SAP as part of Subdvision M of the Pesticide Assessment Guidelines.

In 1983, OPP received its first inquiry regarding the applicability of FIFRA to a genetically modified substance, a bacterium to control ice nucleation on certain kinds of crops. The applicability of FIFRA to a naturally occurring non-ice nucleating bacterium was also considered at that time. The Agency concluded that bacteria which inhibit ice nucleation, whether naturally occurring or genetically engineered, are pesticides and fall under FIFRA jurisdiction (Ref. 1).

Recently, the Agency has addressed the issue of small-scale field testing of nonindigenous and genetically engineered microbial pesticides. As an interim policy, EPA is requiring notification under FIFRA prior to these activities in order to determine the need for experimental use permits. This interim policy, published in the Federal Register of October 17, 1984 (49 FR 40659), is discussed in detail in Unit II.F of this notice.

2. *Concerns related to microbial pesticides.* Microbial pesticides, when naturally occurring and indigenous to the area of intended use, generally raise fewer risk concerns than conventional chemical pesticides. With regard to indigenous microbial pesticides, the Agency has already identified a basis for concern and hence, the need for adequate regulation under FIFRA.

> When a microbe is applied as a pesticide in the environment, great numbers of the microbes are released outside (apart from) their host, at a discrete point in time (day of application), and spread over the biotic and abiotic components of the environment as well as adjacent areas (due to drift); hence, in terms of the number of nontarget organisms exposed, the number of different species exposed (both humans and non-human), and the degree of exposure (number of microbes per nontarget organism), exposure [to the microbe as a pesticide] would probably be greater than under natural conditions. [Pesticide Assessment Guidelines, Subdivision M, p. 45.]

Many of the same types of concerns apply to both indigenous (naturally occurring) microbial pesticides and to nonindigenous and genetically engineered microbial pesticides, namely; infectivity, pathogenicity, toxicity, host range, virulence, and survivability. However, the Agency recognizes that potentially greater risks may exist from the use of nonindigenous and genetically engineered microoganisms as pesticides. For example, they could exhibit a broader host range, a new toxin, enhanced virulence, greater survivability, or greater competitiveness than their indigenous "parent" microorganisms. This could be accomplished by using techniques which alter or manipulate a naturally occurring microorganism's genetic make up (for example, using recombinant DNA (rDNA) techniques).

One of the Agency's major concerns is that risks which are specific to nonindigenous and genetically engineered microbial pesticides would not be identified by the currently established testing scheme for naturally occuring (indigenous) microbial pesticides. Similarly, the Agency is concerned about the stability of the genetic material in a genetically modified microbial pesticide and about the specificity of an inserted gene segment. For example, our current data requirements would yield no information about the characteristics that the inserted genes are intended to express, and the potential for other characteristics to be unknowingly inserted and expressed. A related concern is the potential for transfer of genes from the genetically modified microbial pesticide to naturally occurring microorganisms, and thereby generating new potential risks. This phenomenon is known to occur with the transfer of genes controlling antibiotic resistance to organisms without known contact to antibiotics.

D. Current Regulatory Status of Microbial Pesiticides

The pesticide data requirements, codified at 40 CFR 158.170, are applicable to microbial pesticides, both naturally occurring and otherwise. The Agency believes that these requirements are adequate for the assessment of indigenous microbial pesticides, and provide a basis for evaluating nonindigenous and genetically engineering microbial pesticides as well. However, the Agency believes that additional data or information, on a case-by-case basis, may be necessary to evaluate certain properties of nonindigenous and genetically engineered microbial pesticides. Part 158 explicitly provides the necessary flexibility to require additional data in this situation (§ 158.65) as well as the flexibility to waive data requirements that are not applicable (§ 158.45).

Nonindigenous and genetically engineered microbial pesticides would be subject to additional data requirements or information requirements as needed, depending on the particular microorganism, its parent microorganism, the proposed pesticide use pattern, and the manner and extent to which the organism has been altered or modified. Other requirements could include information on the genetic modification techniques used, the identity of the inserted gene segment (base sequence data or enzyme restriction map of the gene), information on the control region of the genes, a description of the new traits or characteristics that are intended to be expressed, tests to evaluate genetic stability and exchange, and/or selected Tier II environmental fate and toxicology tests.

OPP has broadened its definition of genetic engineering beyond that presented in Subdivision M of the Pesticide Assessment Guidelines to include more than just microbial pesticides modified by rDNA techniques. Therefore, microorganisms modifed by rRNA techniques as well as by cell fusion, conjugation, microencapsulation, microinjection, directed or undirected mutagenesis, plasmid transfer, transformation, etc., are included.

E. Plan for Reviewing and Registering Nonindigenous and Genetically Engineered Microbial Pesticides Under FIFRA

This Unit describes the Agency's plan for reviewing and registering nonindigenous and genetically engineered microbial pesticides in order to estimate or predict potential human or ecological effects and the environmental fate of such mircrobial pesticides after their release into the environment. The Agency is seeking public comments on the merits of this plan. Appropriate revisions in the plan will be made by the Agency after review and evaluation of the comments.

1. *Proposed plan.* The Agency has developed the following strategy for considering the scientific and regulatory issues pertaining to nonindigenous and genetically engineered microbial pesticides:

a. The established procedures and policies for registering pesticides as specified under 40 CFR Parts 150 through 189 will apply to nonindigenous and genetically engineered microbial pesticides.

b. Upon receipt of the application for registration, a **Federal Register** notice will be prepared to announce the receipt publicly. The fact that the submission is for a nonindigenous or genetically engineered microbial pesticide will be highlighted in the notice. The notice will be mailed to interested groups and public comment will be solicited.

c. The data and information requirements specified in 40 CFR 158.65 and 158.170 will apply to nonindigenous and genetically engineered microbial pesticides.

d. Any additional data requirements will be determined on a case-by-case basis depending on the particular microorganism, its parent microorganism, the pesticide use pattern, and the manner and extent to which the microorganism has been altered/manipulated. These additional requirements could include:

i. Information on natural predators and parasites.

ii. Description of the natural habitat of the microorganism.

iii. A comparison of the natural habitat with the proposed use site.

iv. Information on the methods used to genetically alter the microbe.

v. The identity of the engineering techniques used.

vi. Information on the control region of the genes.

vii. A description of the new traits or characteristics that are intended to be expressed.

viii. Tests to evaluate genetic stability, transfer, and exchange.

ix. Selected Tier II environmental fate tests.

x. Selected Tier II toxicology tests.

e. Requests for waivers of any of the requirements of Part 158.170 will be evaluated on a case-by-case basis depending on the particular microorganism, its parent microorganism, the pesticide use pattern, and the manner and extent to which the microorganism has been altered or manipulated.

f. OPP will encourage potential registration applicants to meet with representatives of the Registration Division and the Hazard Evaluation Division (HED) prior to submission of their application to discuss their product and determine whether additional data beyond that specified in Part 158 would be necessary to evaluate the product and whether a waiver is warranted for any of the requirements in Part 158.

g. OPP will seek informal scientific consultation during the pesticide application review process. This may

include ORD, OTS, the National Institutes of Health (NIH) Recombinant DNA Advisory Committee (RAC) and other departments and agencies as appropriate. Any consultation will be within the constraints of OPP's Confidential Business Information (CBI) policies.

h. As needed, OPP will request the FIFRA SAP to consider any significant questions/concerns, the need for additional information/data, and/or to perform a technical review of OPP's decision concerning the request for registration. It may be necessary to request that the SAP form a subpanel of experts to perform this review. This subpanel should include expert representatives from the NIH RAC, EPA's Scientific Advisory Board (SAB), and ORD.

i. OPP will announce the final decision in a **Federal Register** notice. Past experience indicates that the registration process for a new microbial pesticide may vary from 9 months to several years depending upon the particular product, its use pattern, and the completeness of the registration package submitted to EPA.

2. *Long term strategy under FIFRA.* OPP will develop more explicit procedures and/or requirements for evaluating nonindigenous and genetically engineered microbial pesticides. Toward this end, OPP plans to take the following steps over the next few years:

a. OPP will solicit the recommendations of various groups (e.g., government, academic, public interest, and industrial) regarding the evaluation of nonindigenous and genetically engineered microbial pesticides and the environment. This will include further consultation with the participants of the ORD workshop held in 1982 at Gulf Breeze as well as consultation with NIH, USDA, FDA, National Institute for Occupational Safety and Health, and the biotechnology industry. Also, the recommendations from EPA's Biotechnology Workshops will be reviewed and evaluated. (See the Public Record for further information on these Workshops.)

b. Based on findings from the consultations described above, OPP should then be able to better identify additional potential hazards or risks posed by nonindigenous and genetically engineered microorganisms, and the testing or additional research that would be needed to evaluate any potential hazards.

c. EPA will evaluate the question of when and whether data developd on one microorganism can be used to support the registration of another, closely related microorganism (e.g., a closely related strain of the same species), within the constraints of the exclusive use and data compensation provisions of FIFRA.

d. EPA will modify 40 CFR Part 158, Subdivision M, and its regulatory policies and procedures. Current indications are that, at a minimum, certain additional information will be required and perhaps some additional test data to address questions pertaining to host spectrum and stability of engineered agents.

F. Small-Scale Field Testing

Prior to obtaining a registration for a pesticide product, applicants generally need to conduct field studies in order to gather product performance, use, and other data necessary to support the registration of their product. Section 5 of FIFRA provides that a person may obtain an experimental use permit (EUP) authorizing limited use of an unregistered product or use of a registered product for an unregistered use before conducting field studies. 40 CFR Part 172 sets forth the regulations pertaining to EUPs, and Part 158 specifies the data required to be submitted to EPA before EPA will issue an EUP.

The conditions under which an EUP is required are specified at 40 CFR Part 172, which also provides guidance on how to determine whether an EUP must be obtained. Pursuant to § 172.3, when a chemical or indigenous microorganism is being field tested only to determine whether it has value for pesticide purposes or to determine its toxicity or other properties, and the person conducting the test does not expect to receive and benefit in pest control from its use, an experimental use permit has not normally been required.

The Agency has, in the past, exercised considerable judgment and flexibility in determining when an EUP is required. As provided in § 172.3, EPA now presumes that testing of a chemical or indigenous microorganism in small-scale field studies is for the purpose described above. Therefore, an EUP has not normally been required to support such testing. Small-scale field studies are described in § 172.3(a); in summary, they comprise (1) small-scale terrestrial field studies that involve less than 10 acres of land, provided that any food crops involved in or affected by such tests shall be destroyed or consumed only by experimental animals unless a tolerance or exemption from tolerance has been established; (2) small-scale aquatic field studies that involve less than one surface acre of water, provided that waters that are involved in or affected by such tests will not be used for irrigation purposes, drinking water supplies, or body-contact recreational activities. Also, no such test shall be conducted in waters that contain any fish, shellfish, or other plants or animals taken for recreation or commercial purposes and used for food or feed unless a tolerance or exemption from tolerance has been established.

In situations where even small-scale field studies posed a serious environmental or human health concern, EPA has required an EUP. Section 172.3 explicitly recognizes that a wide variety of testing situations may arise, and that a flexible regulatory approach is needed to deal with these situations.

Chemical pesticides have no independent mobility and reproductive capability and therefore when applied in small-scale field studies their potential for causing adverse effects outside the treated area is extremely limited. Microbial pesticides, however, may replicate and spread beyond the site of application. Further, nonindigenous and genetically engineered microbial pesticides may not be subject to natural control or dissipation mechanisms; they may be capable of spreading beyond the site of application with potential adverse effects. Therefore, small-scale field studies with nonindigenous and genetically engineered microbial pesticides would raise many of the same concerns as more extensive use of conventional pesticides.

The agency is considering a change in 40 CFR 172.3 to require that applicants notify the Agency before they conduct small-scale field studies with nonindigenous and genetically engineered microbial pesticides and is interested in comments on the merits of this position. Until the Agency adopts a final approach to these pesticides, which will include the opportunity for public comment, notification is being required as an interim procedure for all small-scale field studies involving the direct release of nonindigenous and genetically engineered microbial pesticides into the environment. This interim procedure does not apply to studies conducted in contained laboratory, growth chamber, greenhouse, or other facilities where there is no direct release of the microbial pesticide into the environment. Notice of this interim policy, with a request for comments, was published in the **Federal Register** of October 17, 1984 (49 FR 40659). Based on the information contained in the notification, the Agency will determine whether an EUP is required.

Notification should include adequate information to allow the Agency to evaluate the small-scale field testing program. Each notification should include the following information, or, where specific information is not submitted, documentation of why it is not practicable or necessary to provide the information:

1. *Background information on the nonindigenous or genetically engineered microorganisms.*

a. Identity of the microbe and means of detection using the most sensitive and specific methods available.

b. Description of the natural habitat of the nonindigenous or parental microorganism, including information on natural predators and parasites.

c. Information on infectivity and pathogenicity to nontarget organisms.

d. Information on the growth and survival of the microbe in the environment (e.g., laboratory or containment facility test data).

e. If the microbe is genetically altered, the following information should be provided in addition to the information listed in numbers 1 through 4 above:

(1) Information on the methods used to genetically alter the microbes, if any.

(2) The identity of the inserted/deleted gene segment in question (host source, nature, base sequence data, or enzyme restriction map of the gene).

(3) Information on the control region of the genes, and a description of the new traits or characteristics that are intended to be expressed.

(4) Information on genetic transfer and exchange with other organisms.

2. *Description of proposed test.*

a. The purpose or objectives of the proposed testing.

b. A detailed description of the proposed testing program, including test parameters.

c. A designation of the pest organism(s) involved (common and scientific names).

d. A statement of composition for the formulation to be tested, giving the name and percentage by weight of each ingredient, active and inert, and where applicable the number of viable microorganisms per unit weight or volume of the product (or other appropriate system for designating the quantity of active ingredient).

e. The amount of pesticide product proposed for use and the method of application.

f. The States in which the proposed program will be conducted, and specific identification of the exact location of the test site(s).

g. The crops, fauna, flora, geographical description of sites, modes, dosage rates, frequency, and situation of application on or in which the pesticide is to be used.

h. A comparison of the natural habitat with the proposed test site.

i. The number of acres, number of structural sites, or number of animals by State to be treated or included in the area of experimental use and the procedure to be used to protect the test from intrusion by unauthorized individuals.

j. The proposed dates or period(s) during which the testing program is to be conducted, and the manner in which supervision of the program will be accomplished.

k. A description of the program for monitoring and containment of the microorganism during the field test.

l. The method of disposal or sanitation of plants, animals, soils, etc., which were exposed during or after the field test.

m. Means of evaluating potential adverse effects and methods of controlling the microorganism if detected beyond the test area.

Upon notification, the Agency will have 90 days to evaluate the notice. Applicants would be free to perform their field test after that time period unless otherwise informed by the Agency.

The Agency also considered two other options when developing the interim policy. First, the Agency could treat nonindigenous and genetically engineered microbial pesticides under existing regulations in the same manner as indigenous microbial pesticides and chemical pesticides and not require an EUP or notification when the field test meets the criteria in § 172.3. This option would not impede innovation or product development of nonindigenous and genetically engineered microbial pesticides. However, it does not address the potential risks from direct environmental release of these microbes; it raises the question of whether the Agency is doing all that it should to prevent unreasonable adverse effects to humans or the environment; and it is inconsistent with the NIH RAC guidelines which require approval before rDNA altered microorganisms under its jurisdiction are tested in the environment. Second, the Agency could require an EUP for all field testing regardless of the acreage involved. While this option addresses the risk from direct environmental release, it could result in time delays and/or increased costs, which, in turn, would impede innovation, and impede the development of microbial pesticides which do not cause unreasonable adverse effects. The Agency believes that the notification procedures set out in the interim policy will allow EPA to evaluate the potential risks involved with field testing nonindigenous and genetically engineered microbial pesticides, while having only a minimal impact on the development of beneficial microbial pesticides for use in the environment.

In issuing the interim procedures on October 17th, 1984, the Agency emphasized that it is an interim policy, subject to revision based on the comments received in response to that notice and the Agency's experiences in implementing the interim policy. In addition, comments received in response to this notice will be considered in formulating a final policy on small-scale field testing of nonindigenous and genetically engineered microbial pesticides.

III. Applicability of TSCA to Products of Biotechnology

A. General Scope of TSCA

TSCA, which was enacted in 1976, provides the Federal Government with authority to address risks posed by a broad range of "chemical substances." TSCA gives EPA authority to assess and control exposure to such substances through all phases of their commercial lifecycle—including research and development, commercial production, use, and disposal. A central feature of the Act is its focus on prevention and its emphasis on information development. By requiring EPA to review new substances before manufacture, and by giving it authority to require testing, TSCA makes it possible to act against risks before harm occurs, rather than after the damage has been done.

1. *Applicability to living organisms.* TSCA provides EPA authority to review and regulate "chemical substances" in general commercial and other applications. As defined in section 3(2) of the Act, a "chemical substance" is "any organic or inorganic substance of a particular molecular identity, including (i) any combination of such substances occuring in whole or in part as a result of a chemical reaction or occurring in nature. . . ." EPA's authority to review living organisms under TSCA is based on this definition. A living organism is a "combination of such substances occuring in whole or in part as a result of a chemical reaction or in part as a result of a chemical reaction or occurring in nature. . . ." Also, any DNA molecule, other nucleic acid, or other constituent of a cell, however created, is "an organic substance of a particular molecular identity."

The conclusion that nucleic acids as well as living organisms are "chemical substances" under TSCA is consistent with the TSCA legislative history, which makes it clear that the term "chemical substance" is to be interpreted broadly. The 1976 House Committee report notes that "the Committee recognizes that basically everything in our environment is composed of chemical substances and therefore the definition of chemical substance is necessarily somewhat broad." In recognition of this fact, the statute explicitly extends the term "chemical substance" to naturally occurring substances (section 3(2)(A)).

Furthermore, EPA believes that TSCA authority over chemical substances extends to biotechnology products—including microorganisms used for purposes subject to TSCA—because Congress intended this Act to provide authority over substances not covered by other health and environmental laws. Other Federal authorities address specific types of products, such as pesticides, drugs, food, and certain agricultural products, However, certain uses of microbes now being developed do not fall under these other authorities. EPA jurisdiction over these new types of products (e.g., microorganisms used to degrade toxic pollutants) is consistent with TSCA's coverage of other chemical substances similarly used.

2. *General types of products subject to TSCA.* TSCA coverage extends to chemical substances and mixtures used in a wide range of general industrial, commercial, and consumer applications. In the context of biotechnology, products potentially subject to review under TSCA include microorganisms in certain physically contained uses (such as the production of pesticides and other commercial chemicals and the conversion of biomass for energy) and in certain uses involving direct release to the environment (e.g., pollutant degradation, enhanced oil recovery, metal extraction and concentration, and certain non-food agricultural applications, such as nitrogen fixation). Section 3(2)(B) of TSCA, however, specifically excludes from the definition of "chemical substances" certain products regulated under other statutes. The most important of the excluded products are pesticides, tobacco and tobacco products, nuclear materials, foods, food additives, drugs, and cosmetics.

In implementing the Act, EPA has interpreted TSCA authority to cover pesticide intermediates, but not food, food additive, drug, or cosmetic intermediates. EPA explicitly stated this position in the reporting rules for the TSCA Chemical Substances Inventory in 1977, published in the **Federal Register** of December 13, 1977 (42 FR 64586). The Agency has followed the policy since then, and it intends to maintain the policy for products of biotechnology. Consistent with this policy, microorganisms used to produce pesticides would fall under TSCA jurisdiction, while the pesticide itself would fall under FIFRA. Microorganisms used to producer foods, food additives, drugs, and cosmetics, although they could be considered "intermediates" subject to TSCA, would not be reviewed under TSCA because they are already reviewed by the Food and Drug Administration (see the FDA Statement of Policy elsewhere in this notice). With respect to nuclear materials, those substances regulated under the Atomic Energy Act (source material, special nuclear material, or byproduct material) would not be subject to TSCA, but microorganisms (or chemical substances produced by microorganisms) that contain radionuclides will be subject to TSCA if used for TSCA purposes. EPA will work through interagency mechanisms to ensure that existing Federal coverage is adequate.

3. *Plants and animals.* The policy proposed in this notice applies to microorganisms, but not to plants and animals. Most genetically engineered plants and animals will be used for food or food-related purposes, which are excluded from TSCA. However, it is also likely that plants and animals will in the future be genetically engineered for non-food uses, such as production of fibers, wool, and rubber. Because of USDA's extensive involvement in this area and the fact that the major Federal expertise on plants and animals lies in USDA and DOI, EPA, is not proposing that living plants or animals, either as whole organisms or *in vitro* cultures, be made subject to TSCA requirements. One exception would be the insertion of gene segments from plants or animals into microorganisms subject to TSCA. In this case, plant or animal genetic material would be subject.

B. Premanufacture Notice Requirements

1. *Description of authority.* Section 5(a) of TSCA requires companies to notify EPA at least 90 days before beginning to manufacture or import a "new chemical substance" for commercial purposes. This reporting requirement is known as premanufacture notification, or PMN. New chemical substances are defined under the Act as substances not listed on EPA's Chemical Substances Inventory, a list of chemical substances in commerce (Ref. 35). Any chemical substance that is not listed by name on the Inventory or that is not "naturally occurring" is "new" and therefore subject to PMN requirements before commercial manufacture. (See Unit III.B.2.b for an explanation of the distinction between new and naturally occurring.)

EPA has implemented TSCA section 5 requirements in a rule published in the **Federal Register** of May 13, 1983 (48 FR 21722) and clarified in a notice published in the **Federal Register** of September 13, 1983 (48 FR 41132). This rule specifies review procedures and information requirements for new chemical substances. The following units describe the proposed applicability of these requirements to genetically engineered microorganisms.

2. *Applicability of PMN requirements to certain products of biotechnology.* Because genetically engineered microorganisms and nucleic acids are neither "naturally occurring" nor listed on the TSCA Inventory, EPA believes they are subject to PMN requirements. The units below propose definitions of "new" microorganisms (which are subject ot PMN review), and "naturally occurring" microorganisms (which are not subject to PMN review) within the context of biotechnology. For a discussion of PMN applicability to isolated nucleic acids, refer to sections III.B.2.c.i and III.D.2.

a. *Summary of applicability.* i. Consistent with its treatment of other chemical substances, EPA has concluded that microorganisms whose nucleic acids were produced through chemical synthesis are "new" and subject to PMN. EPA has also concluded that microorganisms produced by certain techniques that can be used to combine genetic material from organisms that do not exchange genetic material in nature should also be subject to PMN. The techniques that EPA considers as falling in this category include rDNA, rRNA and cell fusion.

Cell microinjection and cell microencapsulation can also be used to combine genetic material across genetic boundaries, but these techniques are just recently being adapted to microorganisms and it is not yet clear whether they could be successfully used to produce commercial substances. EPA requests comment on whether cell microinjection and cell microencapsulation are likely to be successfully used in microorganisms and therefore whether products of these techniques should also be considered "new."

Although EPA has concluded th substances produced by rDNA, rRN

and cell fusion will be subject to PMN, it requests comment on implementation issues. PMN requirements will not be in effect for microorganisms produced through these techniques until the Agency has reviewed public comments and addressed implementation issues.

ii. Certain other techniques of biotechnology are also used to transfer nucleic acid between microorganisms, but the Agency is uncertain whether these techniques will permit combinations that transcend natural boundaries. (EPA acknowledges that genetic boundaries in microorganisms are difficult to define because understanding of gene flow among microorganisms is changing.) Therefore, the Agency is uncertain whether these other techniques should also be considered to produce "new" microorganisms. Techniques in this category are transformation, transduction, transfection, and techniques that promote conjugation and plasmid transfer. The Agency requests comment on the appropriateness of PMN review for microorganisms produced through these techniques.

iii. EPA is uncertain as to whether microorganisms produced through techniques of undirected mutagenesis, such as irradiation or use of chemical mutagens, are "new." On the one hand, microorganisms that are very unlikely to evolve in nature may be produced through these techniques. On the other hand, undirected mutagenesis is similar to natural processes of mutation and it operates within a single gene pool. The Agency requests comment on whether products of this technique should be considered new and subject to PMN.

iv. EPA has concluded that microorganisms found in nature and used commercially without deliberate genetic intervention are "naturally occurring" and therefore are not subject to PMN. The Agency also believes that artificially selected microorganisms fall into the general category of "naturally occurring."

Microorganisms produced through a combination of two or more of the above techniques would be subject to PMN if any single technique considered to produce "new" organisms were employed in their development.

b. *"New" versus "naturally occurring" substances.* In compiling the TSCA Inventory and in keeping to current, EPA distinguishes between "new" substances, which are subject to PMN, and "naturally occurring" substances, which are not. Under the Inventory reporting rules, the Inventory automatically includes (but does not specifically list) all "unprocessed" naturally occurring substances and naturally occurring substances that are processed only by "manual, mechanical, or gravitational means; by dissolution in water; by flotation; or by heating solely to remove water" (40 CFR 710.4(b)). (For the purposes of this notice, these substances are referred to as "naturally occurring".) Because naturally occurring substances are included on the Inventory as existing substances, they are exempt from PMN. On the other hand, chemical substances that are chemically extracted or reacted from naturally occurring substances are not naturally occurring. These substances had to be reported for the Inventory, and, if they are not now listed on the Inventory, they are "new."

This approach reflects a general philosophy that human intervention at a relatively simple level does not remove a substance from the category of naturally occurring. The act of mechanically isolating a substance from nature does not alter its status as "naturally occurring" or make it subject to PMN. In short, two principles must be considered in determining whether a substance is exempt from PMN by virtue of being naturally occurring. First, it must be derived from nature. Second, the extent of human intervention in producing it must be limited.

The Agency believes that a similar logic should be used to determine whether an organism is "new." in principle, naturally occurring organisms are those that (1) exist as a result of natural events or processes, or (2) have been developed as a result of limited manipulation of natural processes. For example, normal events of reproduction or evolution do not produce "new chemical substances" subject to PMN, any more than chemical reactions in nature, unmediated by humans, create "new chemical substances." Similarly, human exploitation of natural reproductive processes, as in the case of traditional animal and plant breeding, does not create a "new chemical substance," any more than does extracting a nonliving substance by manual, mechanical, or gravitational means from a naturally occurring substance.

The techniques of modern molecular biology are revolutionary in that they allow humans to override natural genetic contraints, creating heretofore unknown arrangements of genetic material, and to synthesize genetic material *de novo.* New organisms produced through these techniques may have genomes that do not occur in nature, or gene pools substantially altered from those that would occur through the natural processes of reproduction.

Perhaps the most clearcut examples of techniques that can be used to create "new" organisms are the techniques of R–DNA, R–RNA, and cell fusion which allow the combination of genetic material from organisms that do not exchange genetic material in nature. Organisms produced through these techniques can be considered "new" in the sense that their natural gene pool—i.e., the total genetic information possessed by a population of organisms that naturally exchange genetic material—has been altered.

In theory, PMN requirements could be based strictly on this concept of the natural gene pool. Under this approach, organisms containing genetic material from organisms that do not exchange genetic material in nature or organisms whose gene pools had been otherwise altered, would by definition be "new." However, in practice, this concept would be difficult to apply. Although the theoretical concept of the gene pool is clear, the actual borders of gene pools can be extremely difficult to determine. For plants and animals, the natural gene pool aprpoximates the taxonomic unit "species," but the taxonomic boundaries between species are not always clearly established. Many sexually reproducing organisms that do not interbreed in nature may do so when natural reproductive barriers are removed by human intervention. It is even more difficult to define natural genetic exchange boundaries for prokaryotic organisms (Ref. 5). Their genetic material is exchanged through such mechanisms as conjugation, plasmid transfer, transduction and transformation. While it appears that there are boundaries for genetic exchange among microorganisms, there is no commonly accepted basis for describing these limits.

Given the elusiveness of a generally accepted definition of natural genetic exchange boundaries, and given the importance of human intervention in determining "newness," EPA belives that the most appropriate way to distinguish between "new" and "naturally occurring" microorganisms is by the methods or processes by which they are produced and the level of human intervention involved. Thus, while a biological definition of "new" and "naturally occurring" might in theory be preferable, EPA believes that such definitions may be unworkable for practical reasons. Therefore, the Agency proposes to determine whether a commerical microorganism is now or naturally occurring on the basis of the

techniques used to produce it. (For similar reasons, EPA relied on process-based distinctions for many conventional chemical substances when the TSCA Inventory was compiled. See Refs. 33 and 34. Inventory listing issues are discussed in Unit III.D.4.)

The Agency requests comments on its proposed mechanism for defining new microorganisms, and welcomes suggestions on other possible ways to demonstrate that a product is the equivalent of a naturally occurring substance.

c. *Discussion of specific processes.* The following paragraphs discuss EPA's proposed approach for distinguishing between "new" and "naturally occurring" microbes. The Agency requests comments on this approach. Comments should address:

(1) The appropriateness of defining as "new" microorganisms produced through each of the techniques listed below.

(2) Whether the underlying concepts of gene pool and degree of human intervention support the categorizations.

(3) The potential for risk from microbial products developed through each of these techniques.

(4) The practical considerations associated with a decision on each of the processes listed (e.g., whether any are now in commercial production, whether the technique is definable in meaningful and unambiguous terms, etc.).

(5) The definitions of the techniques in the glossary, including the extent to which they are clear and unambiguous.

(6) Other techniques now being used or under development that should be addressed.

(7) Possible ways of defining genetic boundaries among microorganisms.

(8) Possible ways of differentiating degrees of human intervention.

i. *Chemical synthesis of nucleic acids.* Chemical synthesis techniques are directed at *in vitro* synthesis of nucleic acids from simpler molecules, not mediated by living organisms (Ref. 12). The chemical synthesis of a substance not listed on the TSCA Inventory creates a new chemical substance subject to PMN, regardless of whether an identical substance is naturally occurring. As a result, EPA believes that synthesized nucleic acids and microbes containing synthesized nucleic acids should be subject to PMN requirements, if they are produced for TSCA commercial purposes.

ii. *Microbial products of rDNA, rRNA, and cell fusion, that is, techniques that allow combinations in microorganisms of genetic material from organisms that do not exchange in nature.* EPA believes that microorganisms which were produced by rDNA, rRNA and cell fusion techniques should be considered subject to PMN. The Agency recognizes that these techniques can be used to combine nucleic acids from organisms that exchange genetic material in nature, and therefore can be used to create organisms that theoretically "could" occur in nature, or that could be produced by random mutagenic events. Nevertheless, because these techniques involve direct human intervention at the cellular or subcellular level and allow genetic materials to be combined in organisms that do not naturally exchange genetic material, and given the practicality of a process-based distinction, EPA believes that the resulting organisms should be considered "new." RDNA, rRNA, and cell fusion techniques are defined, for the purposes of PMN requirements, in the glossary.

These techniques may also be used to produce deletions, i.e. losses of DNA sequences. Deletions generally lead to loss or modification of a function (e.g., loss of the frost-promoting activity of "ice-minus" bacteria). While deletions do not involve the mixing of gene pools and generally result in less hardy organisms, there can be circumstances where the loss of function may be significant (e.g. deletion may result in expression of otherwise repressed genes). Therefore, the Agency believes that deletions obtained with these techniques should be subject to PMN requirements. The Agency requests comments on this issue.

EPA believes these same arguments apply to microorganisms produced through other techniques that can combine genetic material from organisms that do not exchange it in nature. Such techniques include cell microencapsulation and cell microinjection. Application of these techniques to microorganisms is in early stages of development. It is too soon to know whether they will be successfully used to produce "new" microorganisms for commercial use. Products of these techniques will be subject to TSCA only if they are applied to microorganisms. EPA requests comment on this issue. Cell microinjection and cell microencapsulation are defined in the glossary of this notice.

iii. *Microbial products of other biotechnology techniques that promote exchange of genetic material.* Other techniques are being used to transfer genetic material between microorganisms; they are usually used among organisms that are closely related. These techniques include transformation, transduction, transfection, and techniques to promote plasmid transfer and conjugation. These techniques are defined in the glossary of this notice.

The Agency has considered the factors which it uses to define "new" organisms; in this case, they do not clearly indicate how the techniques should be categorized. First, it is uncertain whether these techniques permit combinations that transcend natural boundaries. The Agency recognizes that these techniques can be used to transfer genetic material that could be exchanged in nature, and that some of them involve natural mechanisms for gene transfer. However, it has been shown that these techniques, together with artificial selection, can be used to develop microorganisms with particular traits that have not been found in nature (e.g., combinations of plasmids from various organisms in a pollutant-degrading microbe (Ref. 14)).

Second, the fact that these techniques usually involve significant human intervention at the cellular or subcellular level, and the degree to which the transfer mechanisms are artificially promoted, suggest that the resulting organisms should be considered "new."

Given the uncertain and perhaps competing considerations described above, the Agency is unsure as to whether the products of these techniques should be considered "new," and requests comment on the issues.

iv. *Microbial products of undirected mutagenesis.* Certain techniques of biotechnology allow the development of microorganisms not by the combination of genetic material from different organisms, but by the artificial induction of mutations within organisms. These techniques include the longstanding use of undirected mutagenesis techniques to develop mutant microorganisms for the production of foods, pharmaceuticals, and chemicals. Undirected mutagenesis—the random action of chemical and physical mutagens—can be used to produce qualitatively or quantitatively different gene products, including deletion mutations which may cause loss of functions.

The question of whether these techniques produce "new" microorganisms can be viewed from several perspectives. On the one hand, it can be argued that products of undirected mutagenesis are naturally occurring because the changes induced could be detected in natural populations as spontaneous mutations. In addition, the process takes place within the natural gene pool of the population, and does not involve the introduction of

foreign genetic material. Human intervention, in this context, only accelerates the rate of occurrence and captures variation produced by mutation.

On the other hand, it may be argued that mutation plus selection techniques involve chemical processing that fundamentally alters the gene pool of the population of manipulated organisms, even though the gene pool has not been expanded by addition of foreign genetic material. Undirected mutation depends on chemical or other techniques that randomly and artificially induce changes in genetic material at a radically accelerated rate. Selection is used to preserve changes that might have been eliminated by natural processes. Therefore, this process may lead to microorganisms that have been fundamentally altered, resulting in quantitative or qualitative differences in functions unlikely to occur in nature. These arguments would lead to the conclusion that the techniques produce organisms which are "new" and hence subject to PMN.

EPA seeks comment on whether organisms produced by undirected mutagenesis are appropriately considered new, or whether there is a way to distinguish between new and naturally occurring organisms within this group. (Unit III.C of this notice discusses other authorities besides PMN that could be used to address mutated microorganisms; Unit III.D.4 discusses alternatives for addressing the Inventory status of new substances already in commerce.)

v. *Naturally occurring microorganisms.* Microorganisms found in nature and used commercially without deliberate genetic intervention clearly are not "new chemical substances." In addition, EPA believes that microorganisms developed solely through techniques of artificial selection should be considered naturally occurring. Artificial selection techniques impose conditions on the growth of naturally occurring microorganisms with the aim of favoring the multiplication of a particular organism that possesses a desirable trait. These variations result from spontaneous mutations or natural genetic recombinations. Because the individual mutations occur without human intervention, and because it is difficult to define which selection pressures should be considered artificial, EPA does not believe it is feasible or appropriate to consider microorganisms produced through these techniques as new. However, the Agency requests comments on this question.

3. *Chemical substances produced by genetically engineered organisms.* In many cases, genetically engineered organisms will be used to produce chemicals, such as amino acids, peptides, proteins, enzymes, and biopolymers. When these substances are not listed on the TSCA Inventory, they are subject to PMN requirements. However, many chemical substances that are likely to be made in the future by genetically engineered microorganisms are already listed on the TSCA Inventory (e.g., methane, methanol, bacterial amylase, L-phenylalanine), because they are now produced by conventional methods. An argument could be made that these substances are new if produced by genetically engineered organisms, regardless of whether substances of the same name, made by conventional methods, are listed on the Inventory. However, EPA is not proposing at this time that chemical substances produced by genetically engineered organisms should be differentiated from existing products made by conventional methods.

The Agency recognizes that chemical substances produced by genetically engineered organisms could in some respects differ from the substances of the same name produced by other methods—for example, they could have different impurities. However, EPA anticipates that risks, such as those associated with impurities, can be adequately addressed through PMN review of the organism used to make the chemical substance. In reviewing a PMN on a microorganism used to produce a commercial product, EPA will pay special attention to any risks associated with residual organisms, organism fragments, or other impurities present in the final product. EPA will be able to use its section 5 authority to require data on these risks and to regulate the product purity, where necessary.

At the same time, EPA retains the option of defining substances produced by genetically engineered organisms as new, because the Agency is not yet certain whether the potential impurities in these substances will in fact always be reviewed by EPA through other mechanisms. For example, animal and plant cells used to produce new products are not subject to PMN under the proposed approach (refer to Unit III.A.3). If such cells were used to produce a product already on the Inventory, the Agency would not receive a PMN on the cells, and would not be able to review the product for potential risks or impurities associated with the manufacturing process. Therefore, the Agency requests comment on the adequacy of its proposed approach.

EPA could define substances produced by genetically engineered organisms as new by generically modifying all Inventory listings to exclude substances produced by genetically engineered organisms. In this case, PMNs would be required for substances produced by genetically engineered organisms, even if chemical substances with the same name (but produced by conventional methods) were listed on the Inventory. Once PMN review was completed, the substance would be listed on the Inventory by process as well as composition.

Authority to narrow existing Inventory definitions in this way is provided by § 710.1(a) of the Inventory reporting rules, which states that "EPA . . . will revise the categories of chemical substances [on the Inventory] and make other amendments as appropriate." EPA has generally maintained that it can narrow or otherwise modify Inventory listings under this section, as long as in so doing it does not require PMN review of chemical substances already in commerce. To avoid this possibility, the Agency, as part of any action to exclude products of genetically engineered organisms from the Inventory, would request the public to identify commercial chemical substances already being produced by genetically engineered microbes and would retain them on the Inventory.

In conclusion, EPA is not proposing at this time to amend the Inventory to differentiate products of genetically engineered organisms from substances produced by conventional methods. The Agency believes that (a) many of these products will be new under any definition and therefore will be subject to PMN requirements regardless, (b) in most other cases, PMN review of the new organism will be adequate to address risks associated with the synthesis and use of existing products, and (c) it could be administratively difficult to narrow the existing listings without inadvertently delisting existing genetically engineered substances. Nevertheless, EPA intends to consider this option if it finds that information provided in PMNs on the products of genetically engineered microorganisms is generally inadequate, that substances which could cause impurities are in fact not subject to PMN review, or that the PMN review of products of genetically engineered organisms will substantially add to public or environmental protection. Public comments on this issue are welcomed.

4. *Research and development exemption.* Section 5(h)(3) of TSCA exempts new chemical substances produced only in small quantities solely for research and development (R&D) from PMN requirments ("small quantities" must be defined by rule). R&D includes research or testing of a substance's chemical, physical, production, and performance characteristics. As a result, the R&D exemption encompasses a relatively broad scope of activities, including monitored performance testing. Under EPA's PMN rule (40 CFR 720.3(cc)), "small quantities" are those "not greater than reasonably necessary" for the purposes of R&D. Therefore, current requlations put no specific quantitiative limit on the size of R&D activities. These requirements are discussed more fully in the preamble to EPA's PMN rule and in the notice clarifying those rules, published in the Federal Register of September 13, 1983 (48 FR 41132).

The specific provisions of EPA's PMN rule addressing the R&D exemption (40 CFR 720.36 and 720.78(b)) are now subject to stay (48 FR 41132). Until final provisions are developed, persons producing new chemical substances under the R&D exemption must comply with section 5(h)(3) of TSCA and § 710.3(y) of the Inventory rules. In particular, the R&D must be conducted under the supervision of a technically qualified individual, and manufacturers must notify all persons involved in the R&D activities of risks they are aware of.

An important issue for EPA in implementing the TSCA biotechnology program is whether significant risks could occur without Agency review if persons conducted R&D field tests of new microorganisms in an open setting. Concern for small-scale field testing of traditional chemicals is relatively low, because the amounts involved are likely to be small, and the area of application is geographically circumscribed. However, because microorganisms may reproduce and spread in the environment, EPA review at a later commercial stage for these types of products may be too late to prevent widespread exposure.

The possibility of a gap in Federal authority to review field testing of genetically engineered organisms has been widely discussed. It was a major focus of the June 23, 1983 Congressional hearings on the environmental implications of genetic engineering (U.S. House of Representatives Subcommittee on Oversight and Investigations, and Subcommittee on Science, Research and Technology), and has been the subject of other discussions.

Up to the present time, NIH, through the RAC, is the major Federal agency that has reviewed field testing of microorganisms engineered by rDNA techniques. However, the NIH RAC's authority is limited to research sponsored by institutions which receive NIH funds for rDNA research. Its guidelines and review are not binding for privately funded ventures (although voluntary compliance seems to have been effective to date), and it does not address organisms produced through techniques other than rDNA. As a result, it is possible that genetically engineered organisms that would eventually be reviewed under TSCA could be released to the environment as part of a field test before any review had occurred.

To eliminate this possibility, EPA believes that it may be appropriate to require review of new microorganisms before they are tested in an open environment for TSCA purposes. One approach would be to limit the R&D exemption by rule to exclude field testing. Because living organisms might reproduce and spread in the environment, EPA believes that the quantities of organisms involved in field-testing may not be small for purposes of TSCA section 5(h)(3). Therefore, the Agency is considering initiating rulemaking to amend the definition of "small quantities solely for research and development" to exclude living microorganisms directly released to the environment. The effect of this amendment would be to eliminate the PMN R&D exemption for new field-tested microorganisms and ensure their review under TSCA before release.

A number of difficult issues would have to be addressed in order to implement such an amendment to the R&D exemption. For example, clear definitions of "field testing" and "direct release to the environment" would have to be developed, so that researchers could determine what types of activities were subject. Greenhouse testing, for example, may involve releases to the environment which could in some cases be significant. Should greenhouse testing therefore be considered "direct release"? Should EPA set containment standards for greenhouses as a condition for being subject to the R&D exemption? Should EPA incorporate some portion of the RAC guidelines as conditions for the R&D exemption? These and other questions would be addressed during the process of amending the R&D exemption. In the meantime, the Agency welcomes comments and suggestions on these and related issues.

Even under this approach, PMN requirements might not apply to purely academic or noncommercial field tests. TSCA section 5(i) specifies that, for the purposes of section 5, "manufacture" and "process" mean "manufacturing or processing for commercial purposes." Therefore, PMN requirements, including any requirements extended to field testing, might not apply to purely academic field testing conducted for basic research rather than commercial intent. This may create an anomoly, because any risks associated with the field testing of a microorganism are independent of the commercial intent of the tester. The NIH RAC already provides considerable protection, and EPA believes it is appropriate for purely academic research to remain in the domain of the NIH, but the RAC's mandate is limited to federally funded institutions and rDNA research. The issue of academic as well as commercial field testing is under discussion by the Federal Cabinet Council described in Unit IV.B.

The Agency requests comments on the potential risks posed by small-scale field tests, the appropriateness of the approach EPA is considering for addressing these risks, possible alternatives, and the need to address purely academic or other noncommercial field testing.

5. *Other TSCA PMN exemptions.* Section 5(h) provides for several other exemptions for PMN requirements. The most important of these for biotechnology may be section 5(h)(4), which allows EPA by rule to exempt from PMN requirements chemical substances that it finds will not present an unreasonable risk. For example, it might be possible to develop partial or complete exemptions for microorganisms used in closed systems with appropriate methods of containment. EPA requests comments on how the section 5(h)(4) authority could be used to reduce the impact of PMN requirements for specific categories or uses of genetically engineered organisms.

Another important exemption provision may be section 5(h)(1), which provides for an expedited review (45 days rather than the full 90 days) for new chemical substances manufactured for test marketing. This exemption may be appropriate for field tests and other limited commercial applications.

C. Significant New Use Authority

EPA recognizes that any practical approach to defining "new

microorganisms" under section 5 of TSCA will exclude some types of organisms and will therefore not address all potential risks. In particular, the approach outlined in this notice does not provide for PMN review of naturally occurring organisms introduced into environments where they are not native (nonindigenous microbes). In addition, organisms produced through some techniques for manipulating organisms (such as undirected mutagenesis and artificial selection) may not be covered under PMN, depending on the policy that EPA finally adopts. Under some circumstances, these organisms could involve risk to human health or the environment. In fact, the examples of environmental problems from microorganisms involve naturally occurring, nonindigenous forms introduced into new ecosystems (such as the Dutch elm disease). If concern warrants it, these or other risks not covered under PMN review could be addressed under the discretionary authorities of TSCA, such as the significant new use provisions of section 5(a)(2).

Section 5(a)(2) authorizes EPA to determine by rule that a use of a chemical substance is a "significant new use." Once a significant new use rule is promulgated for a specific substance or category of substances, companies are required to notify EPA 90 days before manufacturing or processing the substance for that use. As a result, EPA would be able to review risks associated with the new use before it occurred. This authority could be used to extend PMN-like coverage where concerns for potential risks warrant. For example, if concern for certain new commercial uses of nonindigenous (exotic) microorganisms is sufficient, EPA could define these uses as "significant." Similarly, if organisms produced through undirected mutagenesis are determined to be naturally occurring and therefore not subject to PMN, and if it appears that they may pose potential risks, EPA could address these organisms through a significant new use rule.

EPA is not now proposing to begin a significant new use rulemaking for microorganisms. However, the Agency believes that this authority may prove useful in ensuring review of specific applications of microbes not covered by PMN requirements, and requests public comment on the need for such rules.

D. Implementation Issues

1. *PMN requirements*— a. *Effective date.* After reviewing public comments, EPA intends to issue a statement of policy, to be published in the **Federal Register**. This policy will identify which products of biotechnology are subject to PMN requirements and will announce an effective date for the requirement. The notice will also address the status of an "new" substances already in commerce. Under various alternatives EPA is considering, companies producing such organisms would be required to report their substances to the Inventory or submit a new PMN within a specified period of time. These alternatives are discussed in paragraph b below.

b. *Status of substances now in commerce.* Although EPA does not believe that microorganisms developed through recombinant or other advanced techniques of genetic engineering are now being used for activities subject to TSCA, it recognizes that microorganisms developed through less advanced techniques, such as undirected mutagenesis, are being used for TSCA purposes. Examples of such activities include use of microorganisms for water pollution control and production of commercial chemicals. In fact, the Agency has reason to believe that hundreds or even thousands of mutated strains are now being sold or offered for sale in commerce for non-drug, non-food, and non-pesticidal applications. If EPA determines that new substances produced through these techniques will be subject to PMN, it will have to develop an equitable approach to handling substances already in commerce.

EPA believes that the most appropriate approach may be to allow companies to report genetically engineered substances already in commerce for the TSCA Inventory without going through PMN. This might be done either through voluntary reporting (which might be appropriate if only a few companies were affected), or through a rule under TSCA section 8 (a) and (b), EPA's authority for compiling and keeping current an Inventory of existing chemicals. The Agency believes that this approach is appropriate because its interpretation of the applicability of TSCA to biotechnology is relatively recent, and companies may have entered this area believing in good faith that they were not subject to PMN. An alternative would be to require PMNs from companies for any "new" organisms now in commerce. While this approach would mean that EPA would review these organisms under the PMN authority, it is not consistent with the preventive function of section 5—the uses subject to PMN notification would already have occurred—and could be extremely burdensome on industry and EPA's review resources. Therefore, EPA does not favor this alternative. EPA requests comments on these and other approaches to handling "new" organisms already in commerce, particularly with respect to their practical implications and their implications for health and the environment.

c. *PMN rules and form.* EPA issued a final PMN rule published in the **Federal Register** of May 13, 1983 (48 FR 21722) and clarified it in a notice published in the **Federal Register** of September 13, 1983 (48 FR 41132). EPA is revising several provisions of the rule—relating to the conditions of the R&D exemption and to data requirements in PMNs. It expects to propose revised language in the near future.

The PMN rule defines the chemical substances that are subject to notification requirements, specifies information requirements, establishes procedures for handling confidential business information, establishes EPA review procedures, and implements other provisions of section 5. EPA believes that in most respects these requirements are appropriate for PMNs on new microorganisms. However, certain aspects of the rule and the guidance given by EPA in the preamble may not apply. In particular, EPA does not believe that the PMN form required by the rule will be useful either to submitters of notices on new organisms or to the Agency. Therefore, it would not expect PMN submitters to use this form. In the future, EPA expects to develop generalized guidance for persons submitting PMNs on new microorganisms. In any case, however, companies would be encouraged to contact OTS well before submission of a PMN for more specific guidance on the level of data appropriate for the notice. Unit III.E of this notice describes in general terms the kind of information EPA would expect to see in a PMN on a new genetically engineered organism.

EPA recognizes that there is a growing commercial enterprise that supplies biotechnology research reagents, including commercial production of vectors, linkage sequences, reagents for nucleic acid synthesis, etc. As long as these substances are sold solely for use in R&D activities by the companies purchasing them, they would be exempt from PMN. This is consistent with treatment of other research chemicals under TSCA (see PMN rule, 48 FR 21722, and clarification, 48 FR 41132).

EPA requests comments on the applicability of other aspects of the PMN rule to new biotechnology products.

2. *Applicability to isolated nucleic acid fragments.* Because PMN requirements apply to all isolated "new chemical substances" used for non-R&D purposes, and not simply to the nucleic acid in the new microorganism, these requirements would apply to isolated DNA and RNA fragments and recombinant DNA and RNA (e.g., plasmids), as well as to the "final" recombinant organisms, if they were used or distributed for purposes other than R&D. However, EPA believes that DNA fragments and plasmids will generally be isolated only within the context of R&D activities and therefore would not be subject to PMN requirements.

DNA fragments and plasmids could also be isolated for the purposes of medical testing. As either drugs or medical devices, such fragments would not be subject to PMN requirements.

EPA requests comments on the practical implications of these requirements to persons engaged in commercial biotechnology.

3. *Confidentiality.* Section 14 of TSCA provides for protection of confidential business information submitted under any authorities of the Act. Confidentiality provisions are addressed in detail in the preamble to the PMN rules and in the rule itself (40 CFR 720.80 through 720.90).

4. *Inventory and nomenclature issues.* After a new chemical substance has completed PMN review and entered commercial production, it is listed on the TSCA Chemical Substance Inventory. Subsequently, anyone may make the substance described on the Inventory for purposes subject to TSCA without submitting a PMN. For this reason, Inventory listings, particularly listings of substances of unknown or variable composition or biological materials (UVCBs), are of central importance in defining PMN requirements. To specify the product adequately, these listings include not only the substance name, but also a brief definition. An overly broad definition for a complex substance might allow the manufacture of substances with significantly different properties without PMN review, because they would fall within the general description on the Inventory. An overly narrow definition, on the other hand, might unnecessarily require new PMN submissions because of slight modifications in process or product composition. Any system for listing complex substances on the Inventory, therefore, requires a balance between practical and risk-related considerations.

In listing biotechnological substances on the Inventory, EPA must also decide how to identify isolated DNA and RNA segments and whether to identify nucleic acids within living organisms as nucleic acids or as microorganisms.

EPA intends to work with interested members of the public to develop a listing scheme that defines microorganisms (or nucleic acids) unambiguously, is practical and comprehensible, and ensures that the listings are sufficiently narrow to allow review of legitimately "new" or different microorganisms with the potential for different risks. Currently, a number of microorganisms are listed on the Inventory by genus and species. EPA, however, believes that the way in which these microorganisms are listed is too broad for genetically engineered microbes. More specific descriptors might also go into the Inventory definition of a new microorganism to more clearly identify it and differentiate it from other microbes. For example, a microorganism produced by rDNA techniques might be listed by such factors as the name of the source organism, isolation methods, vectors used, the host, or other features. EPA is now investigating how these or other descriptors could be combined to develop adequate Inventory definitions.

EPA recognizes that much of this information may be confidential, just as the identify of numerous chemical substances now listed on the Inventory is confidential. When a substance's identity is confidential, EPA lists the substance on the publicly available Inventory by a generic name, shielding the confidential information. Inventory confidentially procedures are established in 40 CFR 710.7 and Subpart E of Part 720.

OTS has prepared a background document discussing possible Inventory listing systems in more detail. Persons interested in the nomenclature issue may obtain this document from the OTS Public Information Office at the address listed at the beginning of this notice. The Agency encourages the public to comment on the approaches it is considering and to suggest alternatives.

5. *Issues related to other TSCA authorities.* As discussed above, TSCA provides EPA a wide range of authorities to collect information, require testing of, and regulate exposure to TSCA-covered chemical substances and mixtures. However, EPA believes in general that the PMN authority will provide sufficient oversight of biotechnology products. Nevertheless, several existing requirements under TSCA impose responsibilities on manufacturers, processors, or distributors of all chemical substances. Therefore, these requirements may affect the biotechnology industry. The most importance of these authorities, sections 8(c), 8(e), and 13, are discussed briefly below.

a. *Section 8(c).* EPA issued a final section 8(c) rule, published in the **Federal Register** of August 22, 1983 (48 FR 38178), that requires manufacturers and certain processors of TSCA-covered chemical substances and mixtures to keep records of "significant adverse reactions to health or the environment . . . alleged to have been caused by the substance or mixture." Persons who manufacture or process microbial products that fall under the TSCA definition of "chemical substances" should consult the final section 8(c) recordkeeping rule.

b. *Section 8(e).* Section 8(e) of TSCA requires manufacturers, processors, and distributors of chemical substances or mixtures to notify EPA immediately of any new information "which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment." EPA issued a section 8(e) policy statement published in the **Federal Register** of March 16, 1978 (43 FR 11110) providing guidance on this requirement. Persons manufacturing, processing, or distributing microbial products for TSCA purposes will be subject to this requirement and should consult the policy statement to determine their responsibilities under section 8(e).

c. *Section 13.* Section 13(a) of TSCA prohibits entry into the United States of any chemical substance or mixture that is not in compliance with TSCA statutory and regulatory requirements. To implement this provision, the U.S. Customs Service issued a rule requiring importers of chemical substances in bulk or as part of mixtures to certify at the port of entry (1) that the substances in the shipment are subject to TSCA and comply with all applicable TSCA rules and orders, or (2) that the chemicals are not subject to TSCA (August 1, 1983, 48 FR 34734). EPA issued a notice published in the **Federal Register** of December 13, 1983 (48 FR 55462) interpreting these requirements.

Importers of naturally occurring products, such as lumber, vegetable oils, and natural rubber, must comply with these certification requirements. Thus, importers of microbial products (including for use in R&D) are generally required to certify that their products comply with TSCA, or that they are not subject to the Act. Until PMN requirements for "new" microorganisms are in effect, the importer will be able to certify compliance, regardless of

whether or not the microbial product is genetically engineered.

For further information on section 13 requirements, importers should contact the OTS TSCA Assistance Office.

E. Nature of EPA's PMN Review

OTS has prepared a background document describing possible information that could be submitted in a PMN on a microorganism and a plan for conducting PMN reviews. This document is available from the OTS Public Information Office at the address listed at the beginning of this notice.

The following unit more generally describes the types of information and data that EPA would expect to receive in PMNs for genetically engineered microorganisms, and how OTS intends to conduct PMN reviews for these microorganisms.

1. *Authority to obtain information.* Unlike pesticide and drug statutes, TSCA does not impose *a priori* testing requirements on new chemical substances. The Act requires submitters to provide certain information on chemical identity and exposure to the extent that it is "known or reasonably ascertainable" to the submitter. Submitters must also provide health and environmental test data in their possession or control. These basic information requirements are explained in detail in the PMN rule (48 FR 21722) and clarification notice (48 FR 41132).

EPA has 90 days, extendable to 180 days for good cause, to review the data submitted on a new chemical substance. After the review period has expired, manufacture may begin unless EPA has taken action to control the substance. Where information provided in a PMN is insufficient for a "reasoned evaluation" of the health and environmental effects of the new substance, section 5(e) provides EPA with authority to ban or regulate the substance, pending the development of data. To invoke this authority, EPA must find (a) that the substance may present an unreasonable risk, or (b) that the substance will be produced in substantial quantities, and it may reasonably be expected to enter the environment in substantial quantity or there may be significant or substantial human exposure to it (section 5(e)(1)(A)(ii)(II).)

EPA believes that this section provides adequate authority to control potential risks where specific concerns are identified or exposure may be significant. Because of the high degree of uncertainty associated with the use of genetically engineered organisms in the environment, there may be insufficient data from which to extrapolate or estimate risks. Also, because the organisms may reproduce and grow in the environment, the release of relatively small quantities may lead to substantial exposure. Therefore, in cases where data are insufficient for a reasoned evaluation of the risks and where even relatively limited amounts are released, the section 5(e) authority will be an appropriate tool to obtain data and, if necessary, to regulate genetically engineered organisms used for commerical purposes.

To avoid unnecessary action under section 5(e) or other authorities, persons likely to be subject to PMN requirements should consult EPA early to identify data and other information that might be developed for a PMN. Information needs are discussed in more detail below and in a background document accompanying this notice.

2. *Types of information required.* Because of the wide variety of microorganisms and applications likely to be reviewed in the PMN program, and the absence of generally accepted principles of risk assessment for genetically engineered microorganisms, OTS does not believe that rigid guidance on minimum data is appropriate. For the foreseeable future, OTS intends to decide the level of information appropriate for a "reasoned evaluation" of engineered organisms on a case-by-case basis. However, as the Agency gains experience in the review of nonindigenous and genetically engineered microorganisms and their products under both TSCA and FIFRA, and with the development of risk assessment methods, EPA believes that it will be possible and desirable to develop more specific guidelines on the level of test data and other information that might be submitted and how these data might be used in the evaluation of products of biotechnology.

Data necessary for assessment of a microorganism will vary according to the risk potential of the organism. For example, OTS would generally need more definitive data on the use of a genetically engineered microbe in the open environment than in a closed system. Similarly, the Agency would generally expect more information on organisms that survive and reproduce than for those that will not survive in the environment, or that can be effectively contained. The Agency would be more concerned and would expect more information if the parent or subject organism is pathogenic or toxic to humans, plants, animals, or other microbes; if the parent or subject organism has a function that is ecologically disruptive (e.g., organisms which are extremely competitive for common organic substrates in soil); if the parent or subject organism has a poorly characterized genome; or if the genetic material is unstable or could be transmitted to other organisms.

In all cases, OTS would expect enough information to identify an organism unambiguosly, both to support an assessment of risk and to list the organism on the Inventory. This would include information on (a) sources of the introduced nucleic acids, (b) how the nucleic acids were manipulated, including information about hosts, vectors, etc., and (c) what protein or special function was produced. Data on the parent organisms and the resulting organisms might include physiological, pathological, genetic, cultural, taxonomic, and ecological characteristics.

If an organism is intended for use in physically contained systems, information about growth conditions, containment methods (including emergency back-up systems if the organism is potentially harmful or might be inadvertently released), workplace exposure and worker practices, possible releases, and disposal might be appropraite. If the organism is used to produce commercial substances, OTS would expect data on the purity of the final product and the presence of any residual organisms or contaminants in the product.

If the organism is to be used in the environment, EPA would expect additional information, including information on intended uses, the manner in which the organisms will be applied, and descriptions of the target environment, including the organisms and ecological systems potentially subject to exposure. Testing in microcosms or other simulated environments may be necessary to answer such questions as whether an organism may survive, replicate, be transported, or exchange genetic material with other organisms. Factors that limit the mobility or survivability of the organisms or their genetic material (e.g., via genetic transfer) will also be significant considerations in the risk evaluation. In addition, particularly where organisms may survive, test data such as those described in OPP's Subdivision M Guidelines, described in Unit II of this notice, may be appropriate.

Submitters should also include information developed for an Institutional Biosafety Committee or the NIH RAC, or information related to health and environmental safety developed to comply with other statutes (for example, data developed on an organism originally used for food or drug

purposes might be applicable to later uses of the organism for TSCA purposes).

3. *Conduct of review.* The Agency recognizes the complex issues associated with the review of genetically engineered microorganisms, particularly when released to the environment. Because of the absence of formalized risk assessment methodologies and the limited data base in this area, expert judgment is critical in determining information needs and reviewing potential risks. The review of such organisms may require expertise in such areas as microbial, plant, and animal ecology and pathology; human health and environmental risk assessment of living organisms; and molecular and microbial genetics. Because of the range of expertise that may be required in any given case, OTS intends to supplement its expertise by drawing from other offices within EPA in the review of new microorganisms and to use expert consultants from other Government agencies and academia, where appropriate. The Agency also plans to rely on the federal Biotechnology Advisory Board and an EPA biotechnology advisory committee to provide expert advice and promote consistent review procedures. The details of this proposed advisory system are described in the preface to this FR notice.

Because of the complexity of review issues, and the limited length of the PMN review period, OTS will encourage persons to consult with it before submitting a PMN on a new microorganism. OTS routinely offers manufacturers the opportunity for prenotice consultation concerning PMN submissions; this would be particularly important for biotechnology. During the period of prenotice consultation, OTS would be able to provide guidance on appropriate levels of information for a notice, and manufacturers would be able to describe the specifics of their situation.

Within 5 days of receipt of a notice, OTS will, in accordance with section 5(d)(2), issue a notice in the **Federal Register** stating the identity of the new chemical substance, the category of use, a summary of test data submitted in the notice, and the submitter's identity. When information is claimed confidential, it will be shielded by a generic description. In addition, OTS will maintain a sanitized copy of the PMN in the OTS Public Information Office, at the address listed at the end of this notice. OTS will welcome comments from interested members of the public on the PMN. The public is generally given 30 days to comment on a PMN after publication of the section 5(d)(2) notice.

IV. Intra-Agency, Interagency, and International Activities

A. Coordination Within EPA

Several EPA program offices in addition to OPTS have authority relevant to biotechnology (see the regulatory matrix elsewhere in this notice). The Office of Solid Waste and Emergency Response (OSWER), for example, will be responsible for regulating solid waste produced by companies using biotechnology and is exploring a variety of approaches for using genetically engineered microorganisms to degrade pollutants. The Office of Water has similar responsibility for process effluents, water pollution control, and other water-quality issues. In addition, since 1977 ORD has supported research in the use of engineered organisms to degrade pollutants and in the development of testing protocols for microbial pesticides. This research has formed the basis of OPP's testing guidelines for microbials, described in Unit II of this notice. Over the next several years, ORD will be increasing its research support to the program offices. A description of ORD's research agenda in biotechnology is available as a support document to this notice.

EPA is taking steps to ensure that the biotechnology activities of its program offices are coordinated and the expertise in each of the offices is shared. To achieve this end, EPA has organized an Agency-wide biotechnology committee, made up of senior staff from its various offices. This group will provide policy and scientific support to the different program offices. The panel will provide a mechanism for securing Agency experts for the review of nonindigenous and genetically engineered microorganisms and of technical documents prepared by the program offices.

B. Interagency Coordination

A number of other Federal agencies besides EPA have direct interest in the promotion or oversight of biotechnology. NIH, FDA, USDA, and OSHA have review and regulatory authorities over biotechnology. (USDA in fact has statutes which apply to some of the same organisms EPA regulates, as described in Unit I.B.4). In addition, NIH, USDA, the National Science Foundation, the Department of Defense, and the Department of Energy, among other agencies, have committed significant resources to biotechnology research. The Commerce Department—particularly through the Patent Office, the International Trade Administration, and the National Bureau of Standards—has a major interest in economic and trade aspects of the biotechnology industry. The State Department has also been involved in international policy, scientific, and trade issues. EPA will be cooperating with these agencies as they implement their respective mandates.

EPA's particular concern for interagency coordination lies in the area of health and environmental risks. EPA representatives from ORD and OPTS serve as nonvoting liaison to the NIH RAC; EPA's biotechnology committee described above will be able to provide guidance to the Agency's RAC representatives on specific environmental issues under review by that committee. More broadly, EPA is participating with other Federal agencies in a review by the Cabinet Council on Natural Resources and the Environment on Federal procedures and regulations related to biotechnology. In addition, EPA is working with other agencies to address such issues as mechanisms for sharing Federal expertise and coordinating research and consistency of risk assessment methods and philosophies in the different agencies.

C. International Activities

Biotechnology raises issues of international as well as domestic coordination. Most of the U.S.' major trading partners, including the European Economic Community nations and Japan, are promoting the commercialization of genetic engineering techniques and are reviewing possible regulatory approaches. Because risks from organisms introduced into the environment may be international in scope, and because the manner in which regulations for biotechnology are implemented in the United States will have a direct impact on the competitiveness of U.S. producers in both domestic and world markets, international cooperation is essential. Inconsistent or duplicative domestic regulation will put U.S. producers at a competitive disadvantage. In addition, certification systems which favor domestic products, if adopted by our trading partners, will create substantial nontariff barriers to trade and block market access. Therefore, during the development of the U.S. regulatory procedures for biotechnology products, attention will be paid to the need for achieving consistency in national regulation and international

harmonization. With respect to international harmonization the U.S. will seek to promote scientific cooperation, mutual understanding of regulatory approaches and international agreement on a range of common technical issues such as the development of consistent test guidelines, laboratory practices, and principles for assessing potential risks.

The Organization for Economic Cooperation and Development (OECD) has formed a working group on biotechnology safety and regulation. EPA, through OTS and ORD representatives, is participating with the Departments of State, Agriculture, and HHS on the U.S. delegation. The goal of the OECD biotechnology working group is to review and monitor member nation's biotechnology regulations and risk assessment approaches as a step toward international harmonization.

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(36) Whittaker, R.H. 1969. New concepts of kingdoms of organisms. Science 163:150–160.

VI. Public Record

EPA has established a public record for this statement of policy.

Records related to this document (docket number OPTS–00049) are available for inspection in Rm. E–107, 401 M St. SW., Washington, D.C. 20460 from 8:00 a.m. to 4:00 p.m., Monday through Friday, except legal holidays. The record includes all information considered by EPA in formulating this policy. References cited in Unit VI are available for inspection in Rm. E–107,

401 M St. SW., Washington, D.C. 20460 from 8:00 a.m. to 4:00 p.m., Monday through Friday, except legal holidays. The record includes all information considered by EPA in formulating this policy. References cited in Unit VI are available in the OTS Library, Rm. E–447. The list below describes the information in the record.

1. OTS support and background documents on PMN review information needs and Inventory listing prepared as background for this notice.

2. Consultant reports prepared under contract to EPA used in developing this notice.

3. Statement of Don R. Clay, Acting Administrator, EPA Office of Pesticides and Toxic Substances, before the Subcommittee on Science, Research, and Technology, and Subcommittee on Investigations and Oversight, Committee on Science and Technology, U.S. House of Representatives, June 22, 1983, and related documents.

4. EPA correspondence to persons outside EPA concerning applicability of TSCA to biotechnology.

5. General statement of policy on the regulation of Biorational Pesticides (40 FR 94:23994), May 14, 1979.

6. A list of key events in the development of OPP's regulation of microbial pesticides.

7. A background paper by Betz, et. al., discussing the current regulatory status and the potential hazards posed by genetically engineered microbial pesticides, 1983.

8. Subdivision M of EPA's Pesticide Assessment Guidelines.

9. Final Report: Biorational Workshop, Gulf Breeze, Florida, August 1983.

10. Final Report: Human Hazard Evaluation Testing for Biorational Pesticides, AIBS, July 1980.

11. Memo regarding Applicability of FIFRA or TSCA to Microbial Agents Used to Control Ice Nucleation, from OGC to OPTS, October 26, 1983.

12. Documents related to EPA's biotechnology research strategy and biotechnology workshops developed by the Office of Research and Development.

The docket of the record detailing its specific contents is available in the OTS Reading Room.

DEPARTMENT OF AGRICULTURE

Statement of Policy for Regulations Biotechnology Processes and Products

Summary: This statement describes USDA's regulatory policy regarding use of biotechnology processes and products in agriculture and forestry. It is not an exhaustive set of application requirements. It is intended to assist those entities engaged in biotechnology research, development, testing, evaluation, production, and application in understanding clearly how USDA will approach the regulation of industry's processes and products.

Address: Send written comments by mail or bring comments to: Ms. Karen Darling, Deputy Assistant Secretary, Marketing and Inspection Services, USDA, Room 242–E, Administration Building, 12th and Independence Avenue, SW., Washington, DC 20250. Telephone: Area Code (202) 447–4256.

For Further Information Contact: Dr. James W. Glosser, Assistant to the Administrator, Animal and Plant Health Inspection Service, USDA, Room 300–E, Administration Building, 12th and Independence Avenue, SW., Washington, DC 20250. Telephone: Area Code (202) 447–3580, or Dr. Edgar L. Kendrick, Administrator, Office of Grants and Program Systems, USDA, Room 326–A, Administration Building, 12th and Independence Avenue, SW., Washington, DC 20250. Telephone: Area Code (202) 475–5720.

Introduction: This document is intended to inform the public, scientists, and industry of USDA's current perspective on the regulation of biotechnology processes and products. It describes the regulatory policies, the regulatory framework, and procedures for oversight in agriculture and forestry biotechnology.

Biotechnology is the application of biological systems and organisms to technical and industrial processes. Applied to agriculture and forestry, it is any technique that uses living biological systems to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses. Although the use of living biological systems in the genetic manipulation of organisms dates from man's recognition that animals and crop plants could be selected and crossbred to produce a desired phenotype, during the past half-century, increased knowledge of molecular genetics has added to the sophistication of the genetic engineering of microorganisms. The manipulation or movement of genetic material by recombinant DNA technology arose about a decade ago and is often referred to as "modern biotechnology." The development of monoclonal antibodies from hybridoma techniques is also referred to as "modern biotechnology." The application of modern biotechnologies has made it possible to perform genetic engineering procedures and to develop monoclonal antibody products with an increasing number of applications in agriculture and forestry programs.

Under the jurisdiction provided by numerous statutes (see attached matrix), USDA regulates and conducts research, among other areas, in animal biologics, organisms and vectors, importation and interstate movement of animals, plants, plant products, noxious weeds, seeds, inoculants, and other articles.

The USDA has regulated, overseen, or collaborated in developing a vast number of biotechnological products and processes, new and old. As one example, in the exercise of this regulatory authority, the Animal and Plant Health Inspection Service (APHIS) has issued within the last two years seven licenses under the Virus-Serum-Toxin Act (21 U.S.C. 151–158) for five products produced by modern biotechnology procedures. These licenses were for bacterins, bacterintoxoids, and monoclonal antibodies for immunological or diagnostic uses. Additionally, there are at least 12 new license applications presently under review on a case-by-case basis.

There exists in the agricultural and forestry community a system for the assessment of new cultivar, germplasm, or microorganisms before their commercial release. For decades, the agricultural community, including State, Federal, and industrial researchers, have continuously assessed the impact of plant, animal (including invertebrate), and microbial species in a wide range of cropping and animal production systems, in order to assure stable agricultural production, as well as protection and preservation of the environment. The evaluation and approval procedures currently practiced are outlined in detail in a recent publication from the National Association of State Universities and Land Grant Colleges (NASULGC), Division of Agricultural Committee on Biotechnology.[1]

Although USDA's initial concerns about safety of the modern developments in biotechnology were at the laboratory level, technological progress has extended these safety concerns to field research and industrial applications and production. As a consequence, USDA emphasizes the need for agency oversight at all stages, including research, development, testing, evaluation, production, application, and disposal. To date, no unique or safety problems have been associated with products of genetic engineering, conventional or modern.

[1] Emergency Biotechnologies in Agriculture: Issues and Policies. Progress Report III, November 1984.

I. Mandate of the USDA

The mandate of the USDA, simply stated, is to protect and enhance agriculture and forestry in the United States.

In order to implement this broad mandate, USDA's authority includes responsibility to administer programs relating to research and development; to fund cooperative interaction, marketing and application of products research; to manage, protect, and enhance resources; and to regulate activities. In addition, the Department is chartered to develop new markets for U.S. agricultural commodities, to improve soil and land use techniques, and to improve agricultural production of animals and plants resistant to stress.

II. Historical Perspective

For decades, agriculturists and botanists have introduced nonindigenous organisms into the continental United States, enabling animals and plants not indigenous to North America to become an important part of our major food sources and to provide new ornamental species. USDA conducts research on these organisms and has developed regulatory processes which control the introduction of foreign organisms into the United States based on their potential application to natural and agricultural ecosystems. These processes have effectively safeguarded our agricultural ecosystems against the introduction of foreign pests and pathogens.

Many plant and animal species have also been introduced through various genetic techniques. In fact, scientists have long been able to create new gene combinations within single organisms—even creating new species—through mutagenesis, cross-hybridization, and other breeding techniques. USDA has vast amounts of expertise and scientific data relevant to the evaluation of safety and efficacy of organisms or other products derived from modern biotechnology procedures, because these products are not fundamentally different from products obtained by coventional technology.

The USDA has been in the forefront in the development of modern biotechnology. USDA representatives were active participants at the early meetings and workshops where policy decisions were made regarding recombinant DNA research. In 1976, a committee was formed in USDA for purposes of coordinating research policies among the various agencies in the Department, and between the USDA, the National Institutes of Health (NIH), and the National Science Foundation (NSF). This committee, authorized by the Secretary, is called the Agriculture Recombinant DNA Research Committee (ARRC).

Further, with regard to DNA research the USDA recognized that a uniform set of guidelines should be followed for research regardless of the source of research funding. The Department endorsed and adopted the NIH Guidelines for Research Involving Recombinant DNA Molecules for coordinating interagency research review, and established an internal policy requiring compliance with these guidelines as a condition for receiving funds for research.[2]

III. Regulatory Philosophy

USDA anticipates that agriculture and forestry products developed by modern biotechnology will not differ fundamentally from conventional products.

We believe that the existing regulatory framework of USDA combined with the NIH Guidelines which are mandatory for all research grants are adequate and appropriate for regulating research, development, testing and evaluation, production, and application, of these biotechnology products. Should any new processes or products be shown to require additional regulatory measures, USDA will amend its regulations or will request additional authority.

IV. Existing Regulatory Framework

A. Overview

The various animal quarantine and related laws, namely 21 USC 102–105, 111, 114a–114h, 115–130, 134–134h, and 135–135b, provide the authority to regulate the importation, exportation, and interstate movement of certain animals to prevent the introduction and spread of contagious, infectious, or communicable diseases of animals or poultry.

Under authority of various plant quarantine and related laws, namely 7 USC 147a, 148, 148a–148e, 150aa–jj, 151–164a, 166–167, and 2801–2813, USDA: (1) regulates the importation into and dissemination within the United States of plant pests, nursery stock, and other plants and plant products, and any product or article which may contain a plant pest at the time of movement, (2) inspects plants and plant products offered for export, and (3) issues permits, promulgates quarantines, and regulates movement of noxious weeds into and through the United States or interstate.

The USDA is responsible for all veterinary biologics imported into the United States or shipped in interstate commerce. Pursuant to the Virus-Serum-Toxin Act (21 USC 151–158), USDA regulates the movement and/or production of viruses, sera, toxins, and analogous products intended for treatment of animals, and of organisms, vectors, and products used in research and evaluation.

Within the framework of the Federal Meat Inspection Act (21 USC 601 et seq.) and Poultry Products Inspection Act (21 USC 451 et seq.) USDA regulates the slaughtering and processing of meat and meat food products and poultry and poultry food products derived from animals which have been administered drugs, biologics, or pesticides for experimental testing. These regulations provide that no animal used in research involving an experimental biologic product, drug, or chemical shall be eligible for slaughter at an official establishment unless certain conditions are met. These conditions include demonstrating that the use of such biological product, drug, or chemical will not result in the products of such animals being adulterated.

In addition to the above mentioned specific authorities, USDA cooperates with other federal agencies in determining the regulatory jurisdiction of genetically engineered organisms which fall within the regulatory jurisdiction of more than one agency. In this regard, a Memorandum of Understanding between USDA and EPA, dated October 3, 1984, defines the general principles of cooperation coordination and communication to be utilized between the two agencies. Another Memorandum of Understanding, between USDA and the Food and Drug Administration, published in the Federal Register on June 8, 1982 (47 FR 26458), concerns resolution of jurisdictional questions involving animal biologic products.

The attached regulatory matrix lists the current statutes defining USDA's oversight of biotechnology processes and products. Because the statutory authority of each USDA regulatory agency is unique, there is a need for an overall policy statement to harmonize regulatory activities, eliminate redundancy, and promote cooperation.

Below are discussed the procedures required under the Virus-Serum-Toxin Act of 1913 (21 U.S.C. 151–158), the Federal Plant Pest Act of May 23, 1957 (7 U.S.C. 150aa-150jj), the Plant Quarantine Act of August 20, 1912 (7 U.S.C. 151–164,

[2] "Memorandum to Heads of Department Agencies: Guidelines for Research Involving Recombinant DNA Molecules," October 15, 1979.

166, 167), the Organic Act of September 21, 1944 (7 U.S.C. 147a), the Noxious Weed Act of 1974 (7 U.S.C. 2801 et seq.), the Federal Seed Act (7 U.S.C. 551 et seq.), the Plant Variety Act (7 U.S.C. 2321 et seq.), the Federal Meat Inspection Act (21 U.S.C. 601 et seq.), and the Poultry Products Inspection Act (21 U.S.C. 451 et seq.). These are the authorities USDA expects to be most relevant to present or potential developers and producers of agricultural products of the modern biotechnology.

B. Veterinary Biological Products

Under authority of the Virus-Serum Toxin Act of 1913 referred to below as "VST Act," the USDA has regulatory responsibility over all veterinary biologics imported into the United States or shipped or delivered for shipment interstate. Such products may not be shipped or delivered for shipment interstate or imported if they are worthless, contaminated, dangerous, or harmful. Products prepared for interstate shipment must be prepared in a USDA-licensed establishment under regulations promulgated by the Secretary. Those which are imported into the United States must be imported under a permit issued by the Secretary. The pertinent regulations are found in 9 CFR Parts 101 through 117.

Veterinary biological products are defined in 9 CFR 101.2(w) as "all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live microorganisms, killed microorganisms, and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases of animals."

The licensing provisions are found in 9 CFR 102 of the regulations. A U.S. Veterinary Biological Product License is required for each veterinary biological product authorized to be produced in a licensed establishment.

Requirements for Product License

The issuance of a product license requires the satisfactory completion of the following requirements discussed below to assure purity, safety, potency, and efficacy.

1. A detailed "Outline of Production" that describes all procedures used to produce each serial of a product must be prepared and filed with the USDA.

2. To assist in maintaining uniformity of product, licensees are required to establish a Master Seed of bacteria, viruses, or other microorganisms at a specific passage level to be used as the source of all seed materials. Master Seed and each product are tested to assure purity, safety, identity, and immunogenicity as provided in 9 CFR 113.

3. Ingredients of animal origin used in production must meet accepted standards of purity and quality. Special tests for extraneous agents are required by 9 CFR 113.53 for all materials not subject to heat sterilization.

4. Primary cells and cell lines used for production of Master Seed or vaccine must be tested in accordance with 9 CFR 113.51 and 113.52, respectively. All cell substrates must be shown to be free of bacteria, fungi, mycoplasma, viruses, and other extraneous agents. Cell lines must also be characterized and karyotyped to establish genetic stability through the maximum number of passages used for production. Tumorogenicity and oncogenicity tests must also be conducted on cell lines if direct or indirect evidence indicates that the cell may induce malignancies in the species for which the product is intended.

5. Immunogenicity of vaccines must be supported by statistically valid host animal immunization and challenge studies. These studies are conducted using products produced to represent minimum levels of antigenic mass as provided in the filed Outline of Production. Studies must be designed to correlate the host animal efficacy of the reference product with a potency test that will be used to test each market serial prior to release. Inactivated products are correlated with animal potency tests or quantitative *in vitro* procedures. For live vaccines, host animal immunogenicity tests are correlated with bacterial counts or virus titers. Release of live vaccines for marketing requires a bacterial count or virus titer sufficiently greater than that used in the immunogenicity test to assure that when tested within the expiration period, each serial and subserial has at least a bacterial count two times or a virus titer $10^{0.7}$ greater than that used in the host animal immunogenicity test.

6. Firms are also required to demonstrate their ability to produce each product in a consistently satisfactory manner. Three consecutive satisfactory serials of product must be produced in accordance with an approved Outline of Production in licensed production facilities. Samples of these serials are forwarded to National Veterinary Services Laboratories for prelicense testing to confirm the manufacturer's results.

7. Safety of products must be demonstrated by laboratory and host animal studies. Tests may also include field trials conducted under normal husbandry conditions.

Upon satisfactory completion of all requirements, including review and acceptable of labels, a U.S. Veterinary Biological Product License may be issued.

Products Derived From Modern Biotechnology

Veterinary biological products prepared using modern biotechnological procedures such as recombinant DNA, chemical synthesis, or hybridoma technology will be treated similarly to products prepared by conventional techniques. The unlimited number and kind of products that may result from these modern biotechnology procedures make it impossible to define all requirements in specific terms. Each product is evaluated individually to determine what will be necessary to establish its purity, safety, potency, and efficacy. Scientific considerations may dictate areas of generic concerns or the use of certain tests for specific situations. Special assays, preferably using *in vitro* methods, may be required for potency and stability determinations. Additional tests may be required to assure safety, especially when live microorganisms are present in the biological products.

The Animal and Plant Health Inspection Service (APHIS) will continue to avail itself of additional expertise from the Public Health Service "Interagency Group to Monitor Vaccine Development, Production, and Usage." This interagency committee will be utilized to consider potential human health hazards from the use of veterinary biological products and to review issues such as those arising from the possible use of viruses potentially pathogenic to man or animals.

In order to provide guidance to current or prospective manufacturers employing modern biotechnological methods, the following discussion of points likely to be useful is presented.

1. *Recombinant DNA-Derived Products.* This technology encompasses the isolation, characterization, and insertion of foreign DNA into vectors for the production of foreign gene products in suitable expression systems.

The genetic information coding for the product of interest and other sequences not indigenous to the host are referred to as foreign DNA. The specific cloned nucleotide segment coding for the desired product or other foreign DNA segments must be defined in data supporting each license application. These data must also include a description of the source of the DNA,

the nucleotide sequence, and the restriction endonuclease digestion map.

A vector is a cloning vehicle which provides a suitable origin of replication necessary for production of foreign DNA. Such replicons may be derived from plasmids, bacteriophages, or viruses such as vaccinia, bovine papillomavirus, adenoviruses, of SV40. A restriction endonuclease map of the vector construct describing structural genes, regulatory or promotor regions, insert orientation, and a description of readily detectable phenotypic traits on host cells will be required as supporting data.

Production of functional gene products depends on the efficient expression of cloned DNA-vector complexes in suitable host organisms. Tissue culture cells, bacteria, yeasts, and other cells may be used as hosts for replication of vectors. The mechanisms of transfer, the copy number, and the physical state of the constructed vector inside the host cell, integrated or extrachromosomal, should be described.

USDA's licensing policy for veterinary biological products derived from recombinant DNA technology is evaluated on a product-by-product basis. USDA requires all licensed applicants or products derived from DNA technology to comply with the NIH Guidelines for research involving recombinant DNA molecules.

APHIS has executed a Memorandum of Understanding with the Food and Drug Administration to resolve jurisdictional or definitional questions regarding animal biologic products subject to the VST Act or as drugs under the Food, Drug, and Cosmetic Act (21 USC 301 et seq.). This memorandum was published on June 8, 1982, at 47 FR 26458.

2. *Chemically Synthesized Antigens.* When the product consists of chemically synthesized polypeptides, the appropriate amino acid sequences will mimic the antigenic site or epitope found in the native antigen where one exists. Supporting data shall include type, degree, and persistence of the immune response following administration of the synthetic peptide. Procedures used to increase or prolong an antibody response such as coupling to carrier proteins or addition of adjuvants, must also be described.

3. *Monoclonal Antibody Products.* The specificity and potency of monoclonal antibody products will be compared with that of similar polyclonal antibody products where appropriate. The specificity and sensitivity of monoclonal antibody products must be at least equal to that of antibody products of traditional polyclonal nature.

Monoclonal antibody products must be derived from Master Cell Stocks which meet the requirements of 9 CFR 113.52. Description of cell cloning procedures, preparation, and characterization of cell passages must also be provided.

The Outline of Production must provide a description of all processes including scale-up, ascites fluid or cell culture supernatant preparation, purification, concentration, and inactivation. Mouse colonies must be screened to demonstrate freedom from adventitious agents, especially those detected by the mouse antibody production (MAP) test. If the MAP test discloses the presence of adventitious agents, the product shall not be released unless inactivation procedures approved by Veterinary Services have been performed.

4. *Master Seeds.* Bacterial or viral seed stocks used to prepare veterinary biological products must meet established procedures used to certify Master Seeds for biological products (9 CFR 101.7).

The Master Seed for recombinant DNA derived products may consist of a plasmid or virus carrying the inserted gene. This constructed plasmid is then introduced into the appropriate eukaryotic or prokaryotic expression system selected for vaccine production. Genomic DNA may also be transfected directly into a variety of mammalian cells. Alternatively, in such cases, the stable transfected cell could be considered as the Master Seed.

The establishment of a Master Seed of constructed plasmids or transferred cells requires submission of background information concerning the recombinant DNA procedures used to isolate, purify, and identify genetic material from one source and the modification used for insertion of this material into a new host. Data from cloning, isolation, proliferation, and selection of genetically unique cells would be retained by licensed applicants.

Tissue culture-propagated cells from vertebrate animals used for vector propagation and antigen production must meet the requirements of 9 CFR 113.51 or 113.52.

If a Master Seed has been accepted by Veterinary Services for use in a licensed product, further genetic modifications may be approved with reduced requirements for additional host animal efficacy studies.

Product and Serial Release

Each Outline of Production shall be prepared in accordance with 9 CFR 114.9. Outlines must include procedures to ensure consistency in production and recovery of specific antigenic material. Recovery procedures must include removal or excessive antibiotic levels (9 CFR 114.10) and undesirable fermentation byproducts such as excessive levels of bacterial endotoxins. Serial release tests for purity, safety, and potency with appropriate techniques will be required.

Pursuant to the Act of February 2, 1903, (21 USC 111), USDA has authority to make such regulations and take such measures as may be deemed proper to prevent the introduction or dissemination of the contagion of any contagious, infectious, or communicable disease of animals and/or live poultry from a foreign country into the United States or from one State or territory of the United States or the District of Columbia. Under this authority and the VST Act, the importation into the United States or interstate shipment of organisms and vectors is regulated under Title 9, Code of Federal Regulations, 9 CFR Part 122. Organisms and vectors are defined in 9 CFR 122.1 as entities which may introduce or disseminate any contagious or infectious disease of animals. Such substances may not be shipped interstate or imported without a permit. Permit applications must provide a complete description of the substances, intended use, location of the permittee, and safeguards to be observed. When appropriate, a review is conducted by the Administrator's Parent Committee on Organisms and Vectors. Members of this committee have wide expertise in evaluating safety. Clearance may also require testing in high security facilities at the Veterinary Services Foreign Animal Disease Diagnostic Laboratory, Plum Island, New York.

C. Plants and Plant Products

Pursuant to authority granted by the Federal Plant Pest Act of May 23, 1957, as amended (7 USC 150 aa through 150 jj), and the Plant Quarantine Act of August 20, 1912, as amended (7 USC 151 through 164, 166, and 167), USDA has regulatory authority over the movement into and through the United States of plants, plant products, plant pests, and any product or article which may contain a plant pest at the time of movement. These articles are regulated in order to prevent the introduction, spread or establishment of plant pests new to or not widely prevalent in the United States. The regulations implementing this statutory authority are found in 7 CFR Parts 300 through 339.

The Federal Plant Pest Act and the Plant Quarantine Act would be

applicable to the movement of plants, plant products, and other articles and plant pests developed through biotechnological processes if such plants, plant products, other articles, or plant pests present a risk of plant pest introduction, spread, or establishment.

"Plant Pest," as defined by statute, means any living stage of any insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi, other parasitic plants or reproductive parts thereof, viruses, or any organisms similar to or allied with any of the foregoing, or any infectious substances, which can directly or indirectly injure or cause disease or damage in any plants or parts thereof, of any processed, manufactured, or other products of plants (7 U.S.C. 150aa(c)).

"Movement," as defined by statute, means to ship, deposit for transmission in the mail, otherwise offer for shipment, offer for entry, import, receive for transportation, carry, or otherwise transport or move, or allow to be moved, by mail or otherwise (7 U.S.C. 150aa(g)).

The following discussion describes the current requirements with regard to the movement into and through the United States of plants, plant products, plant pests, and other articles regulated by the Federal Plant Pest Act and the Plant Quarantine Act. In this regard, plant pests are discussed separately from plants, plant products, and other articles which may contain plant pests.

Plants, Plant Products and Other Articles

All nursery stock is prohibited from movement into the United States unless such movement is authorized under a permit issued by USDA (7 U.S.C. 154).

"Nursery stock" is defined to mean all field-grown florists' stock, trees, shrubs, vines, cuttings, grafts, scions, buds, fruit pits, and other seeds of fruit and ornamental trees or shrubs, and other plants and plant products for propagation, except field, vegetable, and flower seeds, bedding plants, and other herbaceous plants, bulbs, and roots (7 U.S.C. 159).

Additionally, USDA restricts through a permit system the importation of plants and plant products not included in the definition of nursery stock when it is determined that the unrestricted importation may result in the entry into the United States of injurious plant diseases or insect pests (7 U.S.C. 159). The entry status of many plants and plant products, and permit requirements have already been determined and are reflected in the regulations.

The determination of whether to issue a permit allowing the importation of plants, plant products and certain other articles, the conditions that must be met prior to entry and distribution of such plants, plant products and other articles throughout the United States is made after an evaluation of the pest risk associated with these plants and plant products.

In the evaluation process, computerized data of plant pests and diseases known to occur worldwide and a literature search of plant pests and diseases associated with the plants, plant products or other articles requested to be imported are conducted to determine:

- What plant pests or diseases are known to infest, infect, or to be carried by such requested plant, plant product, or other articles;
- Whether such plant pests or diseases are new to or not widely prevalent (i.e., "exotic" plant pests or diseases) in the United States; and
- Whether such plant pests or diseases are found to exist in the country where such a plant, plant product, or article is to be exported from.

If it is determined that there is a plant pest or disease in the country of export which is associated with the plant, plant product, or article to be imported, and the pest or disease is exotic, a determination is made as to whether the plant, plant product, or article can be inspected, treated or otherwise handled to ensure that the plant, plant product, or article can enter the United States without risk of introducing or establishing the exotic plant pest or disease. If such treatments or procedures exist, they are imposed as conditions of entry and specified in the permit and regulations. If there are no conditions that can be imposed which are known to be effective to adequately ensure that the exotic plant pest or disease will not be introduced or established, the plant product or article is prohibited entry into the United States.

In addition to determining the conditions of entry for admissible plants, plant products, or other articles, USDA Inspects incoming plants, plant products, and articles that may be carrying plant pests to determine if such shipments are, free of exotic plant pest and diseases and if all of the conditions of importation have been met. If exotic plant pests or diseases are found in the shipment, the shipment is treated if a treatment is available that will be effective in destroying the exotic plant pest or disease, or the shipment is reexported, or the plant and plant products are destroyed under supervision by USDA. In addition, certain propagative plants and plant products are required to be grown under post-entry quarantine on the premises of the importer for a specified time under specified conditions (7 CFR 319.37–7). This is done in order to detect certain exotic plant diseases which, because of their nature, could not be detected upon inspection at the port of entry at time of importation.

Further, USDA is authorized and directed to quarantine any State, Territory, District of the United States, or any portion thereof, when it is determined that such quarantine is necessary to prevent the spread of an exotic plant pest or disease (7 U.S.C. 161). Thereafter, it is unlawful to move any nursery stock or other plant, plant product, or other article capable of transmitting the exotic plant pest or disease except in a manner or method or under conditions prescribed in USDA (7 U.S.C. 161).

Plant Pests

Section 150bb(a) of the Federal Plant Pest Act (7 U.S.C. 150bb(a)), in pertinent part, prohibits the movement of any plant pest from a foreign country into or through the United States or interstate unless such movement is authorized under a permit issued by USDA and is in accordance with such conditions as may be prescribed in the permit. USDA issues permits for the movement of plant pests for experimental or scientific purposes only.

Each request to issue a permit for the movement of plant pests is evaluated to determine what, if any, safeguards can be imposed which would allow the movement of the plant pest without risk that the plant pest would be disseminated. Permits for the movement of plant pests are denied when, in the opinion of USDA, such movement would involve a danger of dissemination of such pest (7 U.S.C. 150bb(b)).

In determining the safeguards necessary to prevent the dissemination of a plant pest, the following factors are considered:

- The plant pest species of the plant pest;
- The known distribution of the plant pest;
- The known or potential economic or environmental consequences should the plant pest become established;
- The colonization potential of the plant pest should there be an accidental release;
- The location of the proposed test facility in relation to the host plants of the plant pest;
- Alternative locations for conducting research;

• How the particular race or strain of the plant pest to be studied interacts with the race or strain of the plant pest that might be found in the area where the test facility is located;

• Whether the value of the information to be obtained from the research outweighs the risk associated with plant pest dissemination;

• Whether alternate and less harmful plant pests could be utilized to obtain the desired research information;

• The mobility and host range of the pest; and

• Availability of effective irradiation procedures or materials in the event of an accidental escape of the pest.

Further, individuals receiving a permit are required to enter into an agreement with USDA stating that they will abide by all conditions imposed by USDA regarding testing, use, and disposal of the plant pest.

Noxious Weeds

In addition to regulating the movement of plants, plant products, and other articles, and plant pests to prevent the introduction or establishment of exotic plant pests, USDA has authority, pursuant to the Noxious Weed Act (7 USC 2801 through 2812), to regulate the importation or movement interstate of noxious weeds.

"Noxious weed" is defined by statute to mean any living stage (including but not limited to, seeds and reproductive parts) of any parasitic or other plant of a kind, or subdivision of a kind, which is a foreign origin, is new to or not widely prevalent in the United States, and can directly or indirectly injure crops, other useful plants, livestock, or poultry or other interests of agriculture, including irrigation, or navigation or the fish or wildlife resources of the Untied States or the public health.

USDA regulates the importation of noxious weeds through a permit system similar to that established and discussed above for plant pests. Regulations in 7 CFR Part 360 designates plants as noxious weeds and establishes procedures for obtaining an import permit.

As previously discussed, the movement into or through the United States of plants, plant products, other articles capable of carrying plant pests, and plant pests derived from techniques of biotechnology would be regulated by USDA as described above if it is determined that such plants, plant products, other articles, or plant pests present a risk of introducing or establishing exotic plant pests in the United States. The following examples illustrate this point.

Nitrogen Fixing. Bacteria of the genus *Rhizobium* have been found to be beneficial to legume plants because they make available to the legume plant an increased amount of nitrogen, important to the growth and development of the plant. Currently, experimentation is being to see if *Rhizobium* can be genetically altered so that it can be introducd in corn and certain other non-legume plants and thereby make available to these plants increased amounts of usable nitrogen. However, one negative effect of *Rhizobium* is that some strains have been shown to product an undesirable yellowing on plants.

To the extent that strains of *Rhizobium* are commercially manufactured and distributed, their movement into or through the United States would be regulated by USDA as described above to prevent the movement of undesirable strains.

Ice nucleation negative bacteria. The bacterium *Pseudomonas syringae,* currently used in ice nucleation research and product development, is a plant pathogen. This disease agent can cause leaf spotting, shoot wilting, and/or blossom drop in a wide spectrum of crops, including stone and pome fruits, citrus, various grasses, lilac, string beans and lima beans. These bacteria are also residents on non-host plants, and, as such, exist on a wide spectrum of non host plants without causing disease. As residents on plants, they foster the development of ice crystals at 32° F. *Pseudomonas syringae* bacteria has been biotechnologically engineered so that it does not promote ice crystal formation until 27° F. or lower. These biotechnologically manufactured bacteria are known as ice nucleation negative bacteria. If non host plants are sprayed with ice nucleation negative bacteria early in the plants' growth, the bacteria occupies sites that would have been occupied by naturally occurring ice nucleation positive bacteria without causing any of the harmful effects found on host plants. This procedure delays frost damage on sprayed plants until the temperature falls to 27° F., thus extending the growing season 2 to 4 weeks and increasing yields.

Since *Pseudomonas syringae* bacteria are plant pathogens, whether biotechnologically engineered or not, its movement into or through the United States would be regulated by USDA as described above.

Detection and Responses to Prevent Establishment of Plant Pests in the United States

In addition to the authority discussed above regarding regulating the movement of plants, plant products, other articles capable of carrying plant pests, and plant pests to prevent the introduction and establishment of exotic plant pests in the United States, USDA also has authority, experience and elaborate procedures established to detect, suppress, and eradicate exotic plant pests should they be introduced or established in the United States.

USDA has authority to declare an extraordinary emergency and take certain regulatory action affecting intrastate commerce (7 U.S.C. 150 dd(b)). The declaration of an extraordinary emergency authorizes the Secretary of Agriculture, after determining that measures being taken by the State are inadequate, to (1) seize, quarantine, treat, apply other remedial measures to, destroy, or otherwise dispose of, in such a manner as the Secretary deems appropriate, any product or article of any character whatsoever, or means of conveyance which the Secretary has reason to believe is infested by, or contains an exotic plant pest; and (2) quarantine, treat, or apply other remedial measures to, in such a manner as the Secretary deems appropriate, any premises, including articles on such premises, which the Secretary has reason to believe are infested or infected by an exotic plant pest.

Pursuant to the Organic Act of September 21, 1944 (7 U.S.C. 147a), USDA is authorized to cooperate with States or political subdivisions thereof, farmers' associations and similar organizations, and individuals to carry out operations or measures to detect, eradicate, suppress, control, or to prevent or retard the spread of plant pests. Utilizing this authority, USDA, in conjunction with its cooperators, has an extensive system for detecting and controlling exotic plant pests and diseases. Procedures are established for communicating, reporting, planning, and managing such exotic plant pests or disease.

When any unusual or significant damage to a crop is observed, a determination is made whether the cause is due to an exotic plant pest. If a determination is made that an exotic plant pest is present in the United States, appropriate federal and state regulatory officials, industry, and the general public are alerted. USDA and its cooperators conduct nursery and field inspections, provide survey coordinators, conduct past surveys to assess the extent of the plant pest infestation, and provide electronic communication which is distributed among all offices involved in the survey and detection efforts.

Once a new plant pest or disease is identified, a search of the literature is conducted and data from specialists is compiled. Once the plant pest surveys are completed to determine whether a plant pest population is established, the extent of the population, and the degree of damage done or which would be done to agriculture, a plan is developed for managing the plant pest. This plan may include regulatory action, eradication, control, suppression, or other activities which may be implemented by USDA and its cooperators.

To the extent that biotechnology results in the development of a plant pest which is released into the environment, USDA would apply these established detection, suppression, or eradication procedures.

USDA is mandated by statute to impose the least drastic action adequate to prevent the dissemination of plant pests new to or not theretofore known to be widely prevalent or distributed within and throughout the United States. This mandate would be applicable to the regulation of plants, plant products or articles capable of carrying plant pests, and plant pests developed through biotechnology.

Other Oversight Mechanisms

Any plant or associated microorganisms that are developed to the point of commercialization, and in which recombinant DNA techniques have been used, will be licensed, certified, or otherwise treated by USDA or state authorities in the same manner as organisms developed by conventional methodologies. A mechanism already exists for the development and evaluation of new crop varieties and associated microorganisms. This mechanism can easily accomodate biotechnology-derived organisms developed by both the public and private sectors. Relevant oversight mechanisms includes, at the national level, the National Germplasm Advisory Board (NGAB), crop advisory committees of NGAB for each crop species, and the national voluntary registration system for new varieties under the Plant Variety Protection Act (7 U.S.C. 2321 et seq.) and Patent and Trademark Law (35 U.S.C. 1 *et seq*). At the state level, oversight mechanisms include local breeders' release boards, state official and trademark variety testing, and state seed certification agencies.

Currently, the USDA utilizes the ARRC, in an advisory capacity, for scientific review of genetically engineered plants and associated microorganisms to be released for research, field tests, and commercial purposes. The ARRC provides scientific evaluation of the impact of the release of these plants into the agricultural research environment. The scientific advisory review uses the NIH guidelines as the basis for evaluation. The continued use of this mechanism depends on its long term applicability to regulatory oversight needs. Once the biotechnology regulatory needs become fully known, further consideration will be made concerning the ARRC's continuing participation in the impact review process.

D. Seeds

The Federal Seed Act ("FSA" 7 U.S.C. 1551 et seq) defines USDA regulatory authority over the importation and interstate shipment of agricultural and vegetable seeds. It does not apply to the production or intrastate distribution of seeds or to seeds other than agricultural or vegetable seeds ("agricultural seeds" are grass, forage, and field crop seeds).

The FSA prohibits interstate shipment of seed that contains noxious weed seeds at levels in violation of the laws of the state of destination or in excess of levels allowed by the Secretary of Agriculture. This provision applies primarily to seed adulterated with noxious weed seed. In a few instances, however, states have determined that a particular variety of agricultural or vegetable seed is itself a noxious weed. In these instances, FSA prohibits the interstate shipment of the seed into those states. The FSA also allows the Secretary to prohibit the importation of agricultural and vegetable seed which is adulterated with noxious weed seed or which is unfit for seeding purposes.

The authority granted to the Secretary by the FSA to prohibit the interstate shipment or importation of seeds which are found to be detrimental to the agricultural interests of the United States applies to seeds genetically engineered with the modern biotechnology to the same extent as any other seeds.

E. Meat and Poultry Products

The Food Safety and Inspection Service (FSIS) is responsible for assuring the safety, wholesomeness, and proper labeling of food products prepared from domestic livestock and poultry.

Although FSIS has no statutory provisions or regulations that address biotechnology directly, the laws and regulations under which the agency operates provide inspection authority to determine the safety and wholesomeness of animals that are slaughtered for human food. FSIS is required by statute to inspect cattle, sheep, swine, goats, equines, poultry, and food products prepared from them which are intended for use as human food to assure that they are wholesome, not adulterated, and properly labeled, marked, and packaged. Congress has conferred the authority to conduct these inspections to FSIS under the Federal Meat Inspection Act (FMIA) and the Poultry Products Inspection Act (PPIA). Inspection under these statutes is mandatory. The cost of inspection, except for overtime and holiday inspection, is required to be borne by the United States. Food, animals, and animal products other than those covered under the FMIA and PPIA may be inspected under a voluntary, reimbursable inspection program established under the Agricultural Marketing act of 1946.

Within the framework of food safety statutes, FSIS has developed regulations for research on experimental animals that are administered animal drugs, biologics, and pesticides (9 CFR 309.17 and 381.75). These regulations state that no animal used in any research investigation involving an experimental biological product, drug, or chemical shall be eligible for slaughter at an official establishment unless certain conditions are met. These conditions include any of several different ways of demonstrating that the use of such biological product, drug, or chemical will not result in the products of such animals being adulterated.

Products Subject to Review. FSIS anticipated that many food animals which are subject to the new techniques of modern biotechnology will not differ substantially in appearance, behavior, or general health from currently inspected cattle, sheep, swine, goats, equines, and poultry. Providing that such living products of biotechnology can be shown not to be adulterated, they would be subject to the same inspection procedures and regulations as traditionally inspected food animals. FSIS is aware that some genetically engineered animals, such as chimeras and some hybrids, may differ substantially from animals that are currently inspected under the FMIA and PPIA. If such animals are ever intended for use as human food and are presented for inspection at an official establishment, a decision would have to be made as to whether such animals were covered under the FMIA of PPIA, and if not, whether FMIA or PPIA should be amended to require mandatory inspection of such animals and their products.

Implementation of Review Authority. FSIS's approach toward the safety

review of food animals resulting from the techniques of modern biotechnology consists, in general, of two phases. The first, an experimental phase, focuses on the experimental aspects of vector administration, gene transfer and gene expression. Since vectors used in animal genetic engineering may be considered as either animal drugs or animal biologics, their administration to food animals would be covered under the current regulations on experimental animals (9 CFR 309.17 and 381.75). The requirement that an animal carcass intended for use as human food not be adulterated may require that certain phenotypic and/or biochemical parameters not be exceeded before the animal can be slaughtered for human food. Depending of future developments, USDA may amend the research animal regulations to provide assurance that the products of animals genetically engineered by certain techniques are not adulterated. The second phase of FSIS's regulatory approach, a commercial phase, would be carried out under existing regulations (9 CFR 301 through 381) and would be product oriented, focusing on commercial development, food production, inspection and labeling.

Additional Considerations

The manner in which regulations for biotechnology are implemented in the United States will have a direct impact on the competitiveness of U.S. producers in both domestic and world markets. Inconsistent or duplicative domestic regulation will put U.S. producers at a competitive disadvantage. Certification systems which favor domestic products, if adopted by our trading partners, will create substantial nontariff barriers to trade and block market access. Therefore, during the development of the U.S. regulatory procedures for biotechnology products, attention is being paid to the need for achieving consistency in national regulation and international harmonization. With respect to international harmonization, the U.S. is seeking to promote sicentific cooperation, mutual understanding of regulatory approaches and international agreement on a range of common technical problems such as the development of consistent test guidelines, laboratory practices and principles for assessing potential risks. In achieving national consistency and international harmonization, regulatory decisions can be made in a socially responsible manner, protecting human health and the environment, while allowing U.S. producers to remain competitive.

Summary

In summary, USDA anticipates that agriculture and forestry products developed by modern biotechnology will not differ fundamentally from conventional products. USDA believes that its existing regulatory framework, combined with the mandatory NIH Guidelines applicable to all research grants, is adequate and appropriate for regulating research, development, testing and evaluation, production, and application of these biotechnology products. The Department will, however, constantly reevaluate its regulatory position as the state of the art of biotechnology evolves. USDA will use a formal and logical process to ensure the continual integration of safety concepts and other principles for the evaluation of biotechnological processes and products in agriculture and forestry for licensing and granting of permits. Should any new processes or products be shown to require additional regulatory measures, USDA will amend its regulations or will request additional authority.

Scientific Advisory Mechanism

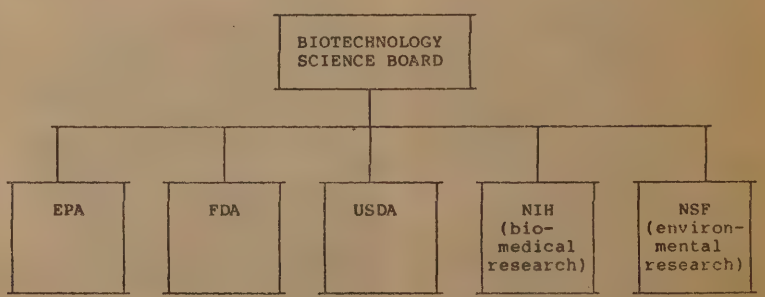
Regulatory decisions must be solidly based on the best available science. The expansion of commercial applications of biotechnology across many fields is a direct outgrowth of a continuously growing science base which draws upon the most fundamental understanding of molecular biology. Scientific assessment of risks associated with biotechnological innovation must draw heavily upon that sophisticated and changing body of knowledge. To supplement agency staff in this essential endeavor, the Cabinet Council Working Group recommends establishment of an independent scientific review mechanism, a two-tiered advisory structure consisting principally of distinguished scientists selected by each of five federal agencies: EPA, FDA, USDA, NIH, and NSF.

The National Institutes of Health Recombinant DNA Advisory Committee (RAC), established in 1974, has performed well in providing scientific assessment of recombinant DNA research proposals submitted from institutions that receive federal funding and has reviewed on a voluntary basis experimental protocols submitted by industry. The current scientific review apparatus is, however, not designed to respond to all the scientific issues surrounding commercialization of biotechnology including the health and broad environmental effects of new commercial processes and products. Hence, the Working Group believes an expanded, coordinated scientific advisory structure is necessary to meet the increased and varied demands for scientific evaluation created by the needs of modern biotechnology.

The objectives to be served by the proposed scientific advisory mechanism are:

- To provide expert advice on scientific issues related to the approval of biotechnology products and research applications;
- To provide a coordinating forum for addressing scientific problems, sharing information, and for consensus building;
- To promote consistency in the development of agencies' review procedures and assessments;
- To promote continuing cooperation among Federal agencies on emerging scientific issues;
- To identify gaps in knowledge.

To accomplish these goals, a two-tiered structure composed of five agency-based scientific advisory committees under a coordinating parent board is proposed.



The Agency-Based Scientific Advisory Committees

The scientific advisory committees will provide detailed scientific review of individual applications or issues that have been submitted to them by federal agencies. Five agencies (EPA, FDA, USDA, NIH, NSF) will sponsor these committees, which will be composed principally of members of the scientific community who possess demonstrated, recognized expertises in disciplines related to biotechnology. The NIH RAC will continue to serve as the scientific advisory committee for biomedical research, operating under procedures specified by the NIH Guidelines for Research Involving Recombinant DNA Molecules. The National Science Foundation will establish and operate a scientific advisory committee to examine the potential effects of environmentally related basic research in biotechnology. That committee will examine questions arising from projects supported by NSF and any other research sponsors requesting its assistance. The activities of the NSF committee will build on the strong ecology and ecosystems research program currently operated by NSF. The committees chartered by FDA, USDA, and EPA will address mainly commerical applications.

Each agency will promptly send to its advisory committee a summary of each application relating to recombinant RNA, recombinant DNA, or cell fusion submitted to it for funding or administrative review, regardless of whether the agency is requesting a scientific review. The advisory committees may decline to receive summaries, or to review, an individual proposal or class of proposals; for example, the NIH RAC has established guidelines which exempt from review some classes of experiments involving recombinant DNA molecules. Any agency of the federal government may request one or more of the scientific advisory committees to review its applications. The parent Biotechnology Science Board may also request that an agency direct its scientific advisory committee to review an application. Any applicant may submit to the head of the appropriate agency a request that its advisory committee review an application.

When a review is completed, the committee will submit its report to the agency that requested the review. It will also send a copy of the report, redacted to delete confidential business information and supplemented with such additional nonproprietary information as is necessary to appreciate the scientific significance of the report, to the parent board for review and comment.

All applications and committee reports containing proprietary information will be protected for confidentiality in accordance with the procedures of the individual agencies requesting scientific review. All procedures will be consistent with agency security procedures, conflict of interest and advisory committee rules, and time constraints.

The Biotechnology Science Board

The parent board will be chartered by the Department of Health and Human Services and will report to the Assistant Secretary for Health. The membership will include two members from each agency-based scientific advisory committee (described above). The board will:

- Receive from each agency a summary of each application relating to recombinant RNA, recombinant DNA, or cell fusion which is submitted to one of the agency-based scientific advisory committees; and, may make a request to the submitting agency that another committee or the parent board itself undertake a review of a specific proposal or classes of proposals.
- Review committee reports, redacted and supplemented as stated above.
- Evaluate review procedures set by the agency-based scientific advisory committees.
- Conduct analyses of broad scientific issues involving rRNA, rDNA, or cell fusion and other processes as needed.
- Develop generic scientific guidelines that can be applied to similar, recurring applications.
- Provide a forum for public concerns.

The board will operate under the time and confidentiality constraints set by the individual agencies; all recommendations of the parent board will be advisor to the committee and/or agency requesting review; and its charter would be subject to renewal after two years.

Glossary of Terms

These definitions are meant to assist the reader. They are not to be considered binding legally on any Federal agency or nonFederal organization.

Animal: Multicellular organism composed of eukaryotic cells with ingestive nutrition and lacking rigid cell walls and photosynthetic ability; members include coelenterates, flatworms, molluscs, segmented worms, arthropods, echinoderms, and vertebrates.

Antibody: A protein (immuinoglobin) produced by humans or higher animals in repsonse to exposure to a specific antigen and characterized by specific reactivity with its complementary antigen. (See also monoclonal antibodies.)

Antigen: A substance, usually a protein or carbohydrate which, when introduced in the body of a human or higher animal, stimulates the production of an antibody that will react specifically with it.

Antiserum: Blood serum containing antibodies from animals that have been innoculated with an antigen. When administered to other animals or humans, antiserum produces passive immunity.

Artificial selection: Techniques imposed on populations of organisms to favor the growth or multiplication of a particular organism.

Attenuated vaccine: Whole, pathogenic organisms that are treated with chemical, radioactive, or other means to render them incapable of producing infection. Attenuated vaccines are injected into the host which then produces protective antibodies against the pathogen to protect against disease.

Bacteria: Any of a large group of microscopic or submicroscopic, prokaryotic organisms having round, rodlike, spiral or filamentous, unicellular or noncellular bodies that are often aggregated into colonies, are enclosed by a cell wall or membrane, and lack fully differentiated nuclei. Bacteria may exist as free living organisms in soil, water, organic matter, or as parasites in the live bodies of plants, animals and other microorganisms.

Biological control agent: Any living organism supplied to or introduced into the environment to control the population or biological activities of another life form.

Biological product: A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product used for the prevention, treatment or cure of diseases or injuries. (Same as biological drug.) (For FDA's regulatory definition, see 21 CFR 600.3(h); for USDA's, see 9 CFR 101.2(w).)

Biological response modifier: Generic term for hormones, neuroactive compounds, and immunoactive compounds that act at the cellular level; many are possible targets for production with biotechnology.

Biologics: Vaccines, therapeutic serums, toxoids, antitoxins, and analogous biological products used to induce immunity to infectious diseases or harmful substances of biological origin.

Biotechnology: Biotechnology is the application of biological systems and organisms to technical and industrial processes.

Cell conjugation: The one-way transfer of DNA between bacteria in cellular contact.

Cell fusion: Formation of a single hybrid cell with nuclei and cytoplasm from different cells.

Cell line: Cell that acquires the ability to multiply indefinitely *in vitro.*

Cell microencapsulation: Techniques using liposomes to entrap and then transfer nucleic acids into cells.

Cell microinjection: A technique in which nucleic acids are injected into a cell.

Chemical synthesis of nucleic acids: In vitro techniques used to synthesize nucleic acids from simpler molecules without mediation by organisms.

Clinical trial: One of the stages in the collection of data for approval of pharmaceuticals, where the drug is tested in humans. (For FDA's regulatory definition, see 21 CFR 50.3(c) or 56.102(c).)

Clone: A group of genetically identical cells or organisms produced asexually from a common ancestor.

Coding sequence: The region of a gene (DNA) that encodes the amino acid sequence of a protein.

Diagnostic products: Products that recognize molecules associated with disease or other biologic conditions of man or animals and are used to diagnose these conditions.

Drug: Any chemical compound that may be administered to humans or animals as an aid in the treatment of disease (For FDA's regulatory definition, see 21 U.S.C. 321 (g).)

Enzyme: Any of a group of catalytic proteins that are produced by living cells and that mediate or promote the chemical process of life without themselves being altered or destroyed.

Escherichia coli (E. coli): A species of bacteria that inhabits the intestional tract of most vertebrates. Some strains are pathogenic to humans and animals. Many nonpathogenic strains are used experimentally as hosts for rDNA.

Eukaryote: A cell or organism with membrane-bound, structurally discrete nuclei and well developed cell organelles. Eukaryotes include plants, animals, fungi and protists. (Compare prokaryote.)

Exons: Any segment of an interrupted gene that is represented in the mature RNA product.

Fermentation: The decomposition of complex molecules under the influence of ferments or enzymes. Fermentation is used in various industrial processes for the manufacture of products such as alcohols, acids, and cheese by the action of yeasts, molds and bacteria.

Food additivie (or food ingredient): A substance that becomes a component of food or affects the characteristics of food and, as such, is regulated by the U.S. Food and Drug Administration. (For FDA's regulatory definition, see 21 U.S.C. 321(s).)

Fungus: Primarily multinucleate organism with eukaryotic nuclei in walled mycelium, absorptive nutrition, and lacking photo-synthetic ability.

Gene: The basic unit of heredity; an ordered sequence of nucleotide bases, comprising a segment of DNA. A gene contains the sequence of DNA that encodes one polyeptide chain (via RNA).

Gene pool: Total genetic information possessed by a population whose members naturally exchange genetic information.

Gene therapy: The insertion of a gene into a patient in a way that it corrects a genetic defect.

Gene transfer: The use of genetic or physical manipulation to introduce foreign genes into host cells to achieve desired characteristics in progeny.

Genetic engineering: A technology used to alter the hereditary apparatus of a living cell so that the cell can produce more or different chemicals or perform completely new functions. These altered cells are then used in industrial production.

Genetic material: DNA, genes, chromosomes which constitute an organism's hereditary material; RNA in certain viruses.

Genome: The basic chromosome set of an organism or the sum total of its genes. The total complement of DNA of a cell carrying the blueprint for organization and function.

Genotype: The genetic constitution of an individual or group.

Germplasm: The total genetic variability available to an organism, represented by the pool of germ cells or seed.

Host-vector system: Compatible combinations of host (e.g., bacterium) and vector (e.g., plasmid) that allow stable introduction of foreign DNA into cells.

Hybrid: The offspring genetically dissimilar parents (e.g., a new variety of plant or animal that results from cross-breeding two different existing varieties, a cell derived from two different cultured cell lines that have fused).

Hybridoma: Product of fusion between myeloma cell (which divides continuously in culture and is "immortal") and lymphocyte (antibody-producing cell); the resulting cell grows in culture and produces monoclonal antibodies.

Intron: A non-coding segment of the DNA of a gene that is removed from the transcribed RNA of cells in higher organisms before translation.

Medical Device: An instrument or apparatus (including an *in vitro* reagent such as MAbs) intended for use in the diagnosis or treatment of a disease or other condition and which does not achieve its intended purpose through chemical action within or on the body. (For FDA's regulatory definition, see 21 U.S.C. 321(h).)

Microorganism: An organism that is a fungus, prokaryote, protist, or virus.

Monoclonal antibodies (MAbs): Homogeneous antibodies derived from a single clone of cells; MAbs recognize only one chemical structure. MAbs are useful in a variety of industrial and medical capabilities since they are easily produced in large quantities and have remarkable specificity.

Monoclonal antibody technology: The use of hybridomas that produce monoclonal antibodies for a variety of purposes. Hybridomas are maintained in cell culture or, on a large scale, as tumors (ascites) in mice.

Mutagenesis: The induction of mutation in the genetic materials of an organism; researchers may use physical or chemical means to cause mutations that improve the production capabilities of organisms.

Mutant: An organism with one or more DNA mutations, making its genetic function or structure different from that of a corresponding wild-type organism.

Mutation: A permanent inheritable change in a DNA sequence or chromosome.

New Drugs: Those not recognized by qualified experts as safe and effective. (For FDA's regulatory definition, see 21 USC 321(p).)

Non-indigenous organism: Naturally occurring organisms placed in environments where they are not native.

Nucleic Acid: Linear polymer consisting of purines or pyrimidine bases bound to a ribose sugar (RNA) or a deoxyribose sugar (DNA) which is in turn bound to a phosphate group.

Organism: Any biological entity, cellular or noncellular, with capacity for self-perpetuation and response to evolutionary forces: includes plants, animals, fungi, protists, prokaryotes, and viruses.

Peptide: A linear polymer of amino acids. A polymer of numerous amino acids is called a polypeptide. Polypeptides may be grouped by function, such as "neuroactive" polypeptides.

Pesticide: (a) any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest, and (b) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant (FIFRA, section 2(u)).

Pharmaceuticals: Products intended for use in humans, as well as *in vitro* applications to humans, including drugs, vaccines, diagnostics, and biological response modifiers.

Phenotype: The appearance or other characteristics of an organism resulting from the interaction of its genetic constitution with the environment.

Physical containment: Procedures or structures designed to restrict the release of viable organisms, degree of containment varies.

Plant: Multicellular organism characterised by eukaryotic cells surrounded by rigid cell walls, photosynthetic ability, and embryonic development; members include mosses, liverworts, and vascular plants (including most terrestrial crop plants).

Prokaryotes: A cell or organism lacking mebrane-bound, structurally discrete nuclei and organelles. Prokaryotes include bacteria and blue-green algae.

Protist: Unicellular, colonial, or multicellular eukaryotic organism lacking embyronic development; plant-like protists include euglena, dinoflagellates, diatoms, algae (except blue-green); animal-like protists include protozoa such as amoeba and paramecia.

Recombinant DNA: The hybrid DNA produced by joining pieces of DNA from different organisms or synthetic DNA together *in vitro*.

Recombinant DNA techniques: Those techniques used to develop recombinant DNA molecules.

Recombinant RNA: Hybrid RNA molecules constructed *in vitro* by joining RNA segments from different organisms (or synthetic RNA); techniques used to produce rRNA molecules.

Recombination: Formation of a new association of genes or DNA sequences from different parental origins.

Somatic cell: One of the cells composing parts of the body (e.g., tissues, organs) other than a germ cell.

Species: A taxonomic subdivision of a genus. A group of closely related, miorphologically similar individuals which actually or potentially interbreed.

Spontaneous mutation: Mutation of unknown causes that occurs as a result of normal cellular operations or interactions with the environment and without direct human intervention.

Transduction: The transfer of bacterial genes from one bacterium to another by a bacteriophage particle.

Transfection: Transformation of eukaryotic and prokaryotic cells or uptake of free viral nucleic acids by cells with the subsequent formation of infective particles.

Transformation: The acquisition of new genetic markers by incorporation of added DNA.

Transgenic: An animal which had a foreign gene transplant is a transgenic animal.

Transposable element: Segment of DNA which moves from one location to another among and within chromosomes in possibly a predetermined fashion, causing genetic change; may be useful as a vector for manipulating DNA.

Undirected mutagenesis: Use of chemical or physical agents to change the sequence of nucleotides in a DNA or RNA in a random, nonspecific manner; examples of mutagens are ethyl methane sulfonate, nitrosoguanidine, and ultraviolet light.

Vector: DNA molecule used to introduce DNA into host cells. Vectors include plasmids, bacteriophage (virus) and other forms of DNA. A vector must be capable of replicating autonomously and must have cloning sites for the introduction of foreign DNA.

Virus: Any of large group of submicroscopic agents infecting plants, animals and bacteria and unable to reproduce outside the tissues of the host. A fully formed virus consists of nucleic acid (DNA or RNA) surrounded by a protein or protein and lipid coat. (For FDA's regulatory definition, see 21 CFR 600.3(h)(1).)

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